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PENICILLIN THERAPY AND CONTROL IN 21 ARMY GROUP

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PENICILLIN THERAPY IN 21 ARMY GROUP

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INTRODUCTION

Earlier this year (February, 1945) the Medical Directorate of 21 Army Group published a booklet—*Memorandum on Penicillin Therapy in* 21 *Army Group*—summarising the properties, laboratory control and uses of penicillin as applied to this theatre of war. This present brochure provides the background on which the initial publication was founded, and is in itself, one feels, a fitting tribute to the very considerable amount of practical work and scientific research put in by those concerned under active service conditions.

How much investigations in the field are affected by tactical necessity and local conditions is frequently not sufficiently appreciated. Movements of units, interchange of personnel and relatively primitive quarters are obvious difficulties militating against sound consecutive research work. In this particular campaign the propinquity of the UK meant minimal holding of a large number of cases—particularly those (*e.g.*, abdominal, orthopædic, thoracic, amputations) in which interest naturally centred to a large degree—for at least the first seven months. And as evacuated cases were in the main treated by a civilian medical service adequate liaison proved difficult to establish.

Nevertheless it will be seen from the following pages that a large volume of work has been encompassed in a relatively short time and it is hoped the results herein recorded may prove of value for immediate application to civilian life and for stimulation of further research. That the work has in the main been carried out by our most experienced war surgeons must greatly enhance the value of the opinions given and the deductions made, for six years of service gives a healthily critical and essentially practical outlook all too often absent in peacetime publications.

It should be frankly admitted at the outset that 21 Army Group have been undeniably fortunate in the supplies of penicillin made available to them. From the outset supplies were generously adequate; for the past five months they have been to all intents and purposes unlimited. Hence it is fair to say that never before has penicillin been used either in prophylaxis or therapy on such a wide scale, and this factor alone adds weight to the evidence contained in the following pages.

One would like to emphasise the prophylactic side of the picture, and particularly the widespread use of parenteral penicillin at the

most forward surgical levels, as this was a new conception at the time of the invasion of Normandy—forced on to us by the tactical demands of the situation which involved a delay of 24–48 hours or more before a wounded man could in the majority of cases receive anything but first aid treatment. In those days, therefore, a generous policy in the use of penicillin was adopted to all wounded; in other conditions its use at first was strictly limited. Early reports from the UK marking the conspicuous absence of wound sepsis seemed to justify the prophylactic programme—although it was fully realised that a certain amount of waste was unavoidable in forward units working under pressure and difficult environmental surroundings. The scheme was therefore continued and slowly enlarged, with results which can in all fairness only be described as eminently satisfactory. It is felt now that given adequate prophylaxis by penicillin in forward areas, a number of cases, approximating to two-thirds of all wounded, will require at subsequent stages of treatment either minimal, or no therapeutic penicillin. It has also been established that penicillin alone, without the added help of the sulphonamides, will give adequate prophylactic protection against wound sepsis.

Looking back, the fight against wound sepsis seems to be, like Gaul, divisible into three parts—the "pre-sulphonamide days" of the BEF when local sepsis was rife and spreading or generalised infections relatively common; the "sulphonamide years" of the MEF and early CMF when the latter severe infections were uncommon, but local sepsis was the rule rather than the exception; and finally the "penicillin days" of the BLA and late CMF when generalised infections from wounds are the greatest rarity and local infections have been reduced to quite small proportions. It is a fascinating metamorphosis and the results recorded herein are indicative of the widespread interest which has been stimulated by the knowledge that the wounded man now, with the bogey of sepsis largely laid, has more than a nine to one chance of living once he reaches surgical aid.

The methods employed both in the prophylactic and therapeutic use of penicillin will emerge in the various articles and have already been given in full in the Memorandum mentioned above. It has been the constant aim in 21 Army Group to evolve methods which facilitate administration both for patients and staff. The extensive use of intramuscular drips affords a good example of this policy. Laboratory control has been insisted upon wherever possible, but it should be realised that this is not available in forward areas, and has added considerably to the already voluminous routine work of the pathological staff of base installations. The valuable work of Major K. E. A. Hughes and of the staff of No. 3 Mob. Bact. Lab. in exercising control over all penicillin issues and in investigating various problems deserves special credit.

The investigations recorded herein have been carried out in British and Canadian hospitals of 21 Army Group and it is a pleasure to record the valued help also given by RAF units. The work has been largely of a practical nature, although researches of a more academic type have also been carried out—some of which will be found described in this brochure. As examples of the type of work concerned, one may mention:—

1. Attempts to simplify and standardise methods of parenteral administration in the field.

2. Trial of various alternatives to the sulphonamides as vehicles for penicillin powder.

3. Use of penicillin in penetrating abdominal wounds (a new departure in this theatre).

4. Use of "slow release" vehicles.

5. Effects of intensive and super-intensive therapy in various conditions.

6. Administration by mouth.

7. Behaviour of penicillin in relation to serous and synovial membranes.

8. Results of local application in infective lesions of the skin, the mouth and accessible body cavities.

9. Relation of various methods of administration to the penicillin content of wound exudates.

10. Attempts to discover the most satisfactory method of eliminating or controlling wound sepsis.

11. The stability of penicillin preparations under various conditions.

12. The effects of various substances on penicillin.

Not all these will be found fully described herein, as investigations are still proceeding and throughout an attempt has been made to avoid generalisations based on inadequate evidence or experience. Certain important subjects (heads, burns, orthopædic and maxillo-facial cases, etc.) are not mentioned or only discussed briefly, either because the "follow up" was lacking or incomplete, or because the specialists who had treated the largest numbers of cases and were most qualified to express opinions have been posted to other theatres.

It is a great pleasure to express my gratitude to Major General E. Phillips, C.B., C.B.E., D.S.O., DMS, 21 Army Group, for his

personal interest in this publication, and to all those Surgeons, Physicians, Pathologists, Medical Officers, Nursing Officers and ORs who have co-operated so willingly and tirelessly in its production.

In particular, I would mention Lt-Col G. A. G. Mitchell (Adviser in Penicillin and Chemotherapy, 21 Army Group), to whom chief credit for this brochure should rightly go, as by his sound common-sense policy, his clear and astute direction and his engaging, cheerful personality, he has provided the incentive which has made the work involved "so easy for so many for so long".

A. E. PORRITT, *Brigadier*,

20 May 1945 — Consulting Surgeon, 21 Army Group

AN INVESTIGATION INTO THE PROPHYLAXIS AND TREATMENT OF WOUND INFECTIONS.

Explanatory Notes prepared by Brigadier A. E. Porritt, Consulting Surgeon, 21 Army Group, and Lt.-Col. G. A. G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy, 21 Army Group.

A preliminary statement on the aim and scope of the investigation may be of value to those who study the evidence in the following reports on wounds. They are based on a 21 Army Group Memorandum on Surgery issued in August, 1944. For reasons already mentioned in the introduction, few surgeons had opportunities to study their cases for the necessary periods until December; and even thereafter, until the investigation was terminated in March, 1945, many were handicapped by moves dictated by tactical necessities.

PURPOSE OF INVESTIGATION

As a preamble it was stated in the Memorandum:—

"Although many bacteriostatic agents are now being used for the prophylaxis and therapy of wound infections, the relative merits of certain of these substances has not been finally determined. In the absence of precise information it is impossible to introduce standard methods for prophylaxis and treatment, and it is proposed to investigate:—

"A. If any advantage is gained by using oral sulphonamide in addition to penicillin as a prophylactic against wound infection.

"B. The relative value of different preparations (or combinations of preparations) in eliminating or controlling infection and so enabling early suture or skin grafting to be carried out."

Further it was stated: "It is a fundamental principle that *all* cases will receive thorough surgical treatment at the earliest opportunity. Appropriate antitoxins will also be given as indicated. The use of bacteriostatic agents is supplementary to these procedures."

METHODS OF INVESTIGATION

A. Each Army Corps normally possesses two CCSs and during a battle they frequently work together. Coming as they do from the same sectors the casualties received by each unit are comparable in most respects, and if the numbers are sufficiently large they provide wounds of every type and grade of severity. In each Corps one CCS was instructed to stop using prophylactic oral sulphonamide and to use penicillin only. The other CCS continued to use both sulphonamide and penicillin. The routine sulphanilamide course is 5 grammes daily for 5 days. In 21 Army Group parenteral and local penicillin are employed in all the more seriously wounded men as a prophylactic measure, and in the less serious cases local penicillin—sulphonamide powder is used (5000 units per gramme). The parenteral dosage employed varies with circumstances. If the forward units are working under stress the giving of frequent injections or intramuscular drips imposes an impossible burden on the overworked staff, and they are allowed to give 100,000 units statim and then 50,000 units every 5–6 hours. When working under less difficult circumstances they use intramuscular drips (100,000 units in 500 ccs isotonic saline daily) or three-hourly injections of 15,000–20,000 units penicillin.

The Field Medical Cards of those patients receiving no sulphonamides were marked "No S", and surgeons in hospitals admitting the cases were asked to compare the results in those who had had penicillin only and those who had been given both penicillin and oral sulphonamide. Any small initial doses of sulphanilamide given before the patients reached a CCS, and the sulphonamide used as a diluent for penicillin powder, had to be ignored, but in the great majority the small amounts used could have produced no significant effect. It was emphasised that if serious infection had developed, or appeared likely to develop, as a result of with-holding sulphonamides, treatment with these drugs should be instituted at once. There is no evidence that anything of this nature happened, yet the habit of giving sulphanilamide is so ingrained in the Army that during the process of evacuation many men who had started off from forward units as "No S" cases were given the drug somewhere en route to the base. For this reason very many cases were rendered valueless for the purpose of this investigation.

Hospital surgeons were asked to keep records of their cases under two headings:—

(*a*) Cases treated with prophylactic penicillin alone.

(*b*) Cases treated with penicillin and oral sulphonamide.

Under each heading cases were to be graded into four categories according to the condition of the wound when first seen in hospital, viz:—

o No evidence of infection;

* Slight infection;

** Moderate infection;

*** Severe spreading infection.

Time intervals are important and records of these were kept when possible, although it was believed that with a sufficiently large number of cases this possible source of variation between the two groups would be equalised.

B. The second problem was studied in hospitals, and to avoid confusing the issue it was suggested that wounds uncomplicated by visceral or skeletal injuries should be selected. It is important to note that otherwise the cases were unselected.

Surgeons in Special Centres obviously could not adhere to these uncomplicated classes, and they were asked to select for contrast treatment wounds as nearly comparable as possible regarding size, structures damaged, degree of infection, etc. Most of these patients, e.g., those with open fractures, were evacuated to the UK at an early stage, and the follow-up information is so incomplete that reports on them cannot yet be supplied.

Alternate cases were to be treated:—

(*a*) With penicillin;

(*b*) With a contrast agent.

The idea was that each surgeon would select what he regarded as the best alternative to penicillin, and it was emphasised that, apart from the chemotherapeutic agent employed, every other controllable factor such as surgery, diet, rest, etc. should be the same in all cases.

Available supplies of various substances such as sulphathiazole, "Marfanil" (P-benzylaminesulphonamide hydrochloride), "V.187" (p-amidinophenyl methyl sulphone hydrochloride), SP powder (sulphathiazole and 1 per cent of proflavine), penicillin powder (sulphathiazole or sulphamezathine with 5,000 units penicillin per gramme), penicillin plasma powder (5,000 units penicillin per gramme), SP Pen powder (sulphathiazole, 1 per cent proflavine, and penicillin 5,000 units per gramme), "Nuflav" (a proprietary sulphonamide-proflavine preparation), etc., were distributed to various units, and attempts were made to secure agents specially requested by any surgeon. A small plant was set up to make electrolytic sodium hypochlorite as two surgeons had suggested they might use it, but in fact it was never required—a possible indication of the absence of heavily infected wounds.

Outline charts and a special proforma to facilitate the keeping of records were provided, and hints given about points to be observed.

The importance of accuracy and uniformity in records was stressed, and the following was suggested as a reasonable assessment for the results of delayed primary and secondary sutures in war wounds:—

Grade I—Success—Wound healed and completely dry at fourteen days (this interval was selected because stitches are sometimes not removed until the eleventh or twelfth day, especially if suture is performed under tension).

Grade II—Partial Success—Wound incompletely healed at fourteen days (some moisture or gaping at areas along suture line, mild stitch suppuration, etc.), but healed and completely dry by twenty-one days.

Grade III—Failure—Wound incompletely healed at twenty-one days.

As a refinement percentage estimates might be made of the partial successes. Thus if at fourteen days a wound 5 inches long was completely healed except for a moist area about 1 inch in extent this was regarded as 80 per cent successful; and in a 10 inch wound a 70 per cent success indicated that healing was incomplete over an aggregate length of approximately 3 inches.

To save space surgeons were told *not* to include individual case records unless they were of especial interest or were used to illustrate some specific point, and it was suggested that results could be shown most concisely in tables. Blank tables were provided as guides, and as many examples of their use are given in subsequent pages they need not be reproduced here. In computing percentage successes in the final column Grades I and II were both included.

They were also told: "There is no desire to limit the scope of your inquiries and any information that may legitimately be extracted from your figures is wanted, remembering always that dogmatic generalisations from very small groups may be misleading. But it is suggested that information on the following points would be valuable, and that whenever possible the conclusions should be supported by figures arranged in tabular form." As these points crop up repeatedly in the reports the questionnaire will be summarised here:—

1. Have you noted any significant differences in the condition of the wounds as compared with those seen in former campaigns? If there are, have you any ideas about the part played by various factors such as previous surgery, time intervals, evacuation, diet, climate, infectivity of terrain, types of missiles, sulpha therapy, prophylactic penicillin, etc.?

2. Can you give a considered opinion of the relative value of penicillin and any contrast agents employed as an aid to early closure or grafting of wounds?

3. Do you think the results with contrast agents were influenced in any way because of previous administration of prophylactic penicillin?

4. Some less seriously wounded men receive only sulpha drugs and no penicillin. Do they show a higher or lower incidence of wound infections than those receiving penicillin? And have you any evidence as to whether or not prophylactic sulphonamide influences the incidence or severity of local wound infections, or tends to prevent generalisation of infection?

5. Have you any comparative figures about the rate of healing and/or recovery of function? Granted that surgery, rest, diet and other controllable factors are equal, are there any differences between the cases treated with penicillin and contrast agents? To obtain this information assessment before fourteen days is necessary as many wounds are completely healed at an earlier date.

6. Are there variations in the rate of healing dependent on an increasing time interval between wounding and operation?

7. Can variations in the results be correlated with the clinical condition of the wounds (clean or dirty) before suture?

8. Do variations in surgical procedures influence the results, *e.g.*, excision or non-excision?

9. What are the effects produced by technical difficulties, *e.g.*, having to suture wounds under tension, closing wounds over subcutaneous bones or tendons, closing wounds in difficult situations (crutch, axilla, sacral area, etc.)? Can you quote successes in these problem cases?

10. Have you figures relating to rates of healing in various areas?

11. If a FB is still present and requires removal at the time of operation does this influence the result?

12. Are the results related to the skill of the surgeon, or may a certain lack of skill be counterbalanced with the aid of a powerful antiseptic agent?

13. If one agent failed have you evidence that the use of another subsequently produced success?

14. Have you seen many sutured wounds in men evacuated before healing was complete? Did their wounds suffer in consequence? Have you formed any ideas about the minimum period a man should be held after he has had a wound sutured?

15. Comparisons between the rates of healing in sutured and unsutured wounds are sometimes illuminating, especially as the latter are usually minor in nature. Can you supply figures on this aspect?

16. Can you correlate laboratory findings and results? Do you think routine wound swabs and cultures provide valuable information or help in deciding prognosis or treatment?

17. Have you reached any conclusions about possible common factors in your failures—insensitive or resistant pathogens, penicillinase—producers present, too much tension, unfavourable situation, pocketing, tenting, secondary infection, retained foreign or necrotic material etc.?

18. Information on any other points.

This was the aim and scope of the investigation. Throughout an attempt has been made to avoid impressions and to substantiate claims by solid figures.

We wish to acknowledge the valued advice and co-operation of Col J. S. K. Boyd, late DDP, 21 Army Group, in planning this investigation.

FACTORS INFLUENCING THE OCCURRENCE OF INFECTION IN WAR WOUNDS

By Brigadier A. E. Porritt, Consulting Surgeon, 21 Army Group and Lt.-Col. G. A. G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy, 21 Army Group.

Most of the reports in our possession contain comments on the condition of the wounds on admission to hospital. On this point there is no divergence of opinion. All are agreed that whether their previous experience was in France (1940), Norway, Egypt, Libya, Greece, North Africa, Malta, or Italy as late as the Spring of 1944, by comparison the wounds seen in this campaign have shown a notable absence of serious sepsis and a reduced incidence of all wound infections.

What is the reason, or rather what are the reasons? All regard penicillin as important, and some regard it as the dominant factor. But nearly all adduce additional reasons. The more important factors will be discussed separately, although a number are more or less inter-related, and the existence of many variables in wounds sustained and treated in the field renders the exact assessment of their individual importance difficult or impossible.

PENICILLIN

All the dangerous pathogens commonly found in war wounds are penicillin sensitive, and if one can get the penicillin into contact with them and maintain it there in an adequate concentration for a sufficient period of time these organisms should be inhibited or destroyed. Prevention is better than cure, so obviously it is desirable to exploit penicillin prophylactically at the earliest practicable stage and in the most effective manner possible.

The basis of the penicillin policy in 21 Army Group since D-day has been prophylaxis. Arrangements were made to use penicillin both parenterally and locally at the most forward surgical levels so that casualties should receive it as soon as practicable after wounding. Arrangements were also made ensuring that penicillin once started, should be continued no matter how or where the patient went, until such time as he had been evacuated or until a surgeon had decided that the treatment could be terminated. This

was a new departure, as the widespread use of parenteral penicillin at this level had not before been attempted, no doubt largely because of shortage of supplies. In many wounds adequate prophylaxis may be provided by local applications, but we are convinced that in the more complicated and lacerated wounds, and in those with retained foreign material, systemic administration in addition is essential to secure the maximum protection. The methods employed are detailed in the "*Memorandum on Penicillin Therapy in* 21 *Army Group*" and need not be restated here.

The recommendations were interpreted generously, and in some cases parenteral penicillin was given when it was unnecessary. This possibility was foreseen when framing the policy, but it was felt that generosity towards the wounded is never misplaced. A somewhat similar policy is accepted without question in using antitoxin in suspected diphtheria and gas gangrene, and handsome dividends justify a high initial expenditure.

There can be no doubt that the incidence and severity of wound infections have diminished because the conviction is so universal amongst those with much experience. The clinical result is most important, yet additional proof might be provided by bacteriological investigation, and such evidence has in fact been produced in the CMF. We possess figures from various sources apparently providing the same proof, but many results must be accepted with reserve since steps were not taken to neutralise any penicillin carried over on the swab or loop. Several have argued that if there is enough to produce bacteriostasis on a plate there must be sufficient left in the wound. This is true at the time, but the penicillin may be absorbed or destroyed before all the pathogens are eliminated—unless the concentration is maintained by further parenteral administration or local applications.

PRIMARY SURGERY

Practically all emphasise the importance of this factor. There is no question that the surgery of war wounds at all levels has improved, for the civilian surgeons turned soldiers five years ago learned much in treading the thorny trail of bitter experience. Yet one fact must not be forgotten in assessing this factor. Most surgeons are reasonably intelligent, and by the time of Alamein in 1942, or even earlier, the basic principles in forward surgery were well established and there have been no fundamental changes since. And another fact is worthy of note, lest it be imagined the balance has been tilted favourably by the weight of previous experience. The majority of the surgeons who came to Normandy last June had no previous experience of forward surgery, although they had been reared in a faith rooted in the Desert rather than in Spain, and had in their midst a small and select band of veterans

from previous campaigns. Actually, apart from the minor mishaps inseparable from initial over-enthusiasm, the primary surgery has been of a uniformly high standard and the results as seen in hospitals have been greatly influenced by its excellence. But few would care to claim that the standard of surgery here is any better, for example, than that achieved by the surgeons following the victorious Eighth Army. Therefore, although we yield to none in the belief that primary surgery is vitally important, we reject the contention that it is the cause of the marked diminution in wound sepsis in this as compared with earlier campaigns.

Not all who read this will be familiar with the basic principles underlying primary surgery in warfare, so they will be enunciated. These principles are observed by forward surgeons in dealing with any wound, naturally supplemented by any additional measures necessitated by associated bony or visceral injuries.

(*a*) *General Treatment.* Rest, reasonable warmth, fluids, morhpine (given intravenously or intramusculary in shocked patients), protective antisera, sulphonamides, oxygen, etc.

(*b*) *Skilful Resuscitation.* The above measures, plus blood and plasma before, during and if need be after operation.

(*c*) *Clothing* is cut away over the wound and not dragged off. The boots are removed in all men with lower limb injuries.

(*d*) *Cleansing* of the skin is done with soap and water, the part shaved if necessary, and then swabbed with flavine or cetavlon.

(*e*) *Asepsis* of the highest standard possible under the prevailing conditions is maintained.

(*f*) *Incision.* The wound may have to be extended to get better access to the depths or to expose pockets. The opening up of undamaged tissue planes is avoided.

(*g*) *Excision* is minimal yet meticulous. No skin is excised unless it is hopelessly damaged. All devitalised muscle, fascia, fat and clot are completely and carefully removed, but the excision of a large margin of viable tissue is a surgical crime. Small, completely-detached bone fragments are removed; large, completely-detached bone fragments are left in situ. The prophylactic value of this step cannot be over-estimated.

(*h*) *Foreign Material* is all removed if possible. Blind explorations in search of deep-lying metallic bodies not properly localised are definitely unwise. It is particularly desirable, however, to remove all pieces of clothing, incendiary fragments, and similar dangerous and irritating substances.

(*i*) *Protection of Blood and Nerve Supplies.* Tension must be relieved by adequate division of the deep fascia, and pressure produced by displaced bone fragments dealt with.

(*j*) *Haemostasis* is secured by ligatures and not by packs. The latter are very very seldom necessary.

(*k*) *Skin Sutures* are never employed by forward surgeons unless the patient is to be held for at least 4—5 days or more, *e.g.*, men with abdominal wounds. Deeper structures may have to be sutured, *e.g.*, the muscle layers in a sucking chest wound, or the synovial membrane in an open joint injury.

(*l*) *Dressings* are non-adherent and not over-voluminous. An excess of soft paraffin or masses of wool hinder evaporation and tend to produce a soggy wound. Tight bandages are dangerous. Dressings are not changed until the patient reaches a hospital, unless any signs of complications develop, or unless for some reason evacuation is delayed; unnecessary dressings greatly increase the risks of secondary infection.

(*m*) *Rest* is important. In all the larger limb wounds, with or without bony injury, the part is immobilised with an appropriate splint. Any plaster casts applied are both padded and split, and bandages or circular turns of adhesive tape are not applied underneath.

(*n*) *Prophylaxis.* The effective performance of the above procedures together constitute an effective prophylactic measure, but additional protection is provided by penicillin.
Penicillin is applied locally in the form of penicillin-sulphathiazole powder (5,000 units per gm), and parenteral administration in addition is always instituted in men with large, lacerated or contaminated wounds, and in those with vascular, visceral or bony injuries.

Pre- and Post-Operative Care. These, like primary surgery, have become standardised, but there has been one change since the earlier days of the war. Nursing sisters now work at the most forward surgical levels, and have proved of inestimable value in raising the standards of nursing care and in improving the morale of the wounded. The resuscitation and transfusion services have maintained the same high standard of excellence here as in previous campaigns.

SULPHONAMIDES

This is the most vexed problem of all, and is the one real source of divergent opinion. Everyone agrees that these drugs are very valuable in the treatment of most varieties of spreading or generalised infections complicating war wounds. But do the sulphonamides have any effect either on the incidence or severity of local infections? Many surgeons had ample opportunities to study the effects of good surgery and adequate sulphonamides (oral and local) when in

Africa. We take the liberty of quoting Lt.-Col. E. A. Jack's remarks on the subject (Quarterly Penicillin Report, Oct.—Dec., 1944) because he expresses so well what many believe to be true:

"Wounds received at forward base hospitals have changed materially since the beginning of the war and may be divided into three phases.

"Firstly the pre-sulphonamide phase of 1940, before the routine administration of sulphonamides in forward areas. The average wound received during the retreat in France was an angry inflamed affair with an area of cellulitis extending deeply into the tissues of an ill patient.

"Secondly the sulphonamide phase seen best in the casualties from the Western Desert where routine, adequate administration from the time of wounding was highly organised. Cellulitis and the extension of the infective process into undamaged tissues was comparativly rare, but the wounds were usually the site of an active local infection even after excision.

"Finally, the present penicillin phase, in which the state of the wound itself has, without any doubt, shown a remarkable change for the better. Infection may still be present but, in the average wound that has been adequately trimmed, it is depressed to an almost negligible quantity."

Most will agree that the above is a fair and accurate assessment. Sulphonamides usually prevent spreading and generalised infections, but have little or no effect on the incidence or severity of local infections. Some details and figures about the comparative prophylactic values of penicillin and sulphonamides are given in the section on "Penicillin and Sulphonamides in Prophylaxis". (See next article).

CLIMATE

Several surgeons point out that in the Desert soldiers often had insufficient water either for drinking or washing. Dehydration is not seen here, but the men who fought through the mud in Belgium, Holland and Germany last winter, and who occupied water-logged slit trenches, were contaminated with dirt much more dangerous than the Desert variety.

Infected ulcers, so familiar to many as "Desert sores", are comparatively rare in this theatre. For some reason—too much UV light, excessive sweating, constant abrasion by dust or sand, the prevalence of flies, dehydration, avitaminosis, or what you will—skin resistance to infection was low in Africa. The fly-menace is to a certain extent bound up with the climate. Except last autumn in the area between Tilly and Caen flies have not been troublesome here, whereas in Africa and Italy they frequently were.

The evidence favours the view that the climate in NW Europe is more favourable from the point of view of avoiding infection than it is in Africa. On the other hand the climate here has not changed appreciably in five years, yet the incidence of wound sepsis has changed very appreciably between 1940 and 1945.

CLOTHING

Woolen materials are more liable to harbour infection than cotton. Therefore any retained clothing in wounds sustained here is potentially more dangerous as a source of infection.

TERRAIN

Few mention this factor in their reports, possibly because everyone is so well aware of the high infectivity of the soil in this part of the world. Major J. D. MacLennan, when conducting investigations into gas gangrene in this theatre, examined swabs taken from a number of large, contaminated wounds before treatment, and isolated Cl. Welchii from about 80 per cent of them. In similar wounds examined by the same observer in the Desert, Cl. Welchii were isolated in 28–30 per cent of cases.

This is dangerous ground to fight over, and those who were here in 1940 know that the incidence of sepsis (including serious conditions such as gas gangrene) was high, even in those days before the retreat began and all services became disorganised. Unfortunately all records were apparently lost, and accurate figures in consequence are lacking.

At many places in Normandy dust was a great problem as many emergency roads were "bulldozed" through orchards and fields, and not a few of these passed close to field medical units.

DIET

The feeding here has probably been better than in any previous campaign, and compares very favourably with the "hard tack" (tinned meat, biscuits, "M and V" and brackish water) common enough in the Desert, especially in the earlier stages. The standard of general health and fitness here have been unusually good and the morale excellent. Yet many of us never felt better or more fit in our lives than when in the Desert.

HYGIENE : IMMUNISATION : WELFARE

All these factors, so important in maintaining the soldier's health and morale at the highest pitch, have been very efficiently organised in this campaign.

TIME AND DISTANCE

Two time-distance factors require consideration:—

1. The interval between wounding and primary surgery.

2. The interval between primary and secondary surgery.

These in turn are related to important subsidiary factors such as rest, frequency of dressings, etc.

1. Most agree that from the viewpoint of preventing infection this interval is the more important. We have already stated that primary surgery, closely similar to that at present performed, has been the accepted routine since at least the time of Alamein in 1942. From then on all the big battles have been initiated from established or consolidated positions and the earliest and costliest phases have approximated to static warfare, with the surgical cover well forward and well placed. The formation and increasing use of FSUs was another important help in this respect. The majority of the casualties under such circumstances reach the forward surgeons within twelve to fourteen hours, and it is true to say that this interval has not been significantly different here.

2. The second interval, especially in the Desert when the lines were extended, was often much longer in the earlier days than any in this theatre. It is probable that the almost universal occurrence of moderate to severe wound sepsis seen in ME hospitals was due to this factor. The long and exhausting journeys, the lack of rest, the frequent pain, the difficulties of providing suitable invalid diet and sufficient fluids, and the irrepressible tendency to change dressings at each staging post, all led to inevitable infection. In the first Wavell campaign it was not uncommon for ten days or more to elapse between wounding and the time a man arrived in hospital, and he might have passed through six to ten units en route. This state of affairs steadily improved, although intervals of five to six days remained common.

By the time of Alamein evacuation was more rapid, partly because of better transport facilities on the ground and in the air and partly because of the shorter distances. It would, therefore, be important to know something of the condition of wounds seen at that time. At the time of the great battle itself one of us remembers a particular convoy well, as it contained eighty-eight orthopaedic cases, a larger number than usual. All were received in hospital within three to four days of wounding, all had been adequately treated and splinted by forward surgeons, the great majority had been given the routine course of prophylactic sulphanilamide, and the wounds had not been redressed. Despite this, practically all the wounds were infected to a greater or lesser degree. In that group two men had severe anaerobic cellulitis and one died. Another had a penetrating wound of the knee with condylar fractures and a suppurative

arthritis that subsequently necessitated amputation. These men were as well treated and had as easy and rapid a passage as most of our wounded men now, but the condition of their wounds was very different from what we have become accustomed confidently to expect.

Later, the intervals fluctuated with the location of the fighting, but even when the front was far away the ever-increasing use of air transport kept the average times down to limits not dissimilar to those common here today. Air transport of casualties has been used more widely in this than in any other campaign but mainly in evacuating patients to the UK. This factor cannot influence the most important time interval—that between wounding and primary surgery.

From figures supplied in various reports the following facts emerge:—

1290 wounds were sutured within one to seven days after wounding.

863 wounds were sutured eight days or more after wounding.

As it is the general rule to suture most wounds one to two days after admission it is clear that about 40 per cent of the casualties do not now reach a hospital where definitive surgery is possible until about a week or more after wounding. From late 1942 onwards the average intervals in other theatres have not been greater.

MISSILES AND NATURE OF WOUNDS

This factor receives scant attention, not because the nature of the missile and the resulting wound is unimportant, but because the types of injuries in pre-penicillin days were not significantly different from those occurring now. At one phase there may be more mine injuries, at another more mortar wounds, at another a preponderance of shell or bullet wounds, but taken all over there are as many serious wounds here as there have been anywhere. Indeed, several experienced forward surgeons have been commenting upon the unusually high proportion of severe wounds encountered in recent months. This cannot be regarded, therefore, as a factor in the changing incidence of infection.

CONCLUSION

The chief factor in the diminution of sepsis in war wounds is penicillin.

PENICILLIN AND SULPHONAMIDES IN PROPHYLAXIS

By Brigadier A. E. Porritt, Consulting Surgeon, 21 Army Group, and Lt.-Col. G. A. G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy, 21 Army Group.

Men unfortunate enough to be wounded soon experience the effects of another weapon, the quasi-scientific blunderbus of modern prophylaxis and therapy. It is all for their good, no doubt, yet it is fortunate they are sufficiently young and vigorous to withstand the treatment. They get a selection of morphine, coramine, adrenaline, ephedrine, pitressin, ATS, AGGS, penicillin, sulphonamides, plasma, blood, salines, and fluids inserted and aspirated with annoying persistence through various orifices; not to mention that curious combined food, drink and medicine—"compo" tea.

Is all this really necessary? Is there any prophylactic advantage, for example, in giving penicillin—and AGGS—and sulphonamides? Serum is not our Aunt Sally, but it would be desirable to know if combined prophylaxis with penicillin and serum offers any advantages over penicillin alone, especially as serum is not altogether innocuous. This point may have been determined already; if so the knowledge has not crossed the Channel.

An investigation was instituted here last August in an attempt to discover if any advantage is gained by using oral sulphonamide in addition to penicillin as a prophylactic against wound infection. Details of the scheme are given in the notes on "An Investigation into the Prophylaxis and Treatment of Wound Infection." It seemed simple enough. But one has to reckon with those sensitive, allergic souls who never risk reading official documents; and with those who, having acquired the sulphonamide habit, cling to it with a touching, if uncritical, fidelity. Add to this the flavour imparted by frequent staff changes, and some of the casemates confronting the field investigator loom squatly through the fog.

We hoped to obtain information about 4,000 to 5,000 cases. In fact we hardly got 1,200 because so many casualties leaving forward units as "No S" cases failed to escape receiving sulphonamides somewhere en route to the base. The figures, however, are adequate for our purpose.

The following table gives the results compiled from seventeen different reports. The assessment of the degree of wound infection

was made by the surgeons who first examined the wound after admission of the patients to hospitals. The majority of the group receiving "penicillin only" had parenteral as well as local penicillin. A smaller percentage in the penicillin plus sulphonamide group had parenteral penicillin, but all had local penicillin treatment in addition to the routine prophylactic course of sulphanilamide by mouth. The third group had all received sulphonamides by mouth, and probably most had also had local applications of this agent. The miscellaneous group had received nothing at all, or only local applications—usually sulphathiazole with 1 per cent proflavine.

RESULTS FOLLOWING THE USE OF VARIOUS PROPHYLACTIC AGENTS

Agents	Total Cases	Degree of Infection				Percentage 0 and *
		0	*	**	***	
Penicillin only; parenteral and/or local	497	298	165	28	6	93.1
Penicillin—parenteral and/or local; and sulphonamides by mouth .	480	275	159	37	9	90.4
Sulphonamides by mouth, and usually locally	157	74	41	25	17	73.2
Miscellaneous	43	19	16	7	1	81.4
TOTALS	1177	666	381	97	33	88.9

The last two groups do not concern us greatly and may be dismissed briefly. The number of serious infections (***) was much higher in the "sulphonamide only" group than in any of the others, but these were practically all in prisoners who had had no or inadequate primary surgery; for this reason it would be misleading to make comparisons with the other groups. The miscellaneous group apparently consisted almost entirely of men with minor wounds.

Coming now to the main groups, those who had prophylactic penicillin only, and those who had both penicillin and sulphonamide, it is obvious that the former suffered not at all from the absence of sulphonamide. Indeed they were probably better off, considering they escaped the unwelcome side effects inevitably associated with sulphonamide administration in a proportion of cases.

A number of surgeons comment on the difficulties of distinguishing between no (0) and slight (*) infections, so in the final column both grades were included when computing the percentages. For

all practical purposes these may be regarded as clean wounds, and in this series at least nine out of ten wounds fall into this category. Only fifteen out of 977 cases had infections classed as severe (***), considerably less than 2 per cent. This, we believe, conveys an accurate picture of the cases treated with penicillin, with or without sulphonamide, in this theatre.

The difference between the results in the first two groups is too small to be significant, yet it may be of some importance that, as far as can be determined, a higher proportion of the "penicillin only" group received parenteral penicillin. Thus, in 126 "penicillin only" cases, 117 had parenteral and local penicillin, and nine had local penicillin alone; whereas in 152 cases who had both penicillin and sulphonamide, ninety had parenteral and local penicillin, and sixty-two had local penicillin alone. If these are a fair sample of the whole it suggests that the "penicillin only" group contained a higher proportion of men with severe wounds, as these are the ones more likely to receive parenteral penicillin.

In assessing results one should consider all relevant factors such as the severity of the wounds, the degree of contamination, primary surgery, time intervals, etc., besides any chemotherapy employed. As stated in the explanatory notes, however, it was believed that by getting sufficient numbers of cases from forward units receiving men with the same types of wounds sustained in the same areas, these other factors would cancel themselves out. This is a reasonable assumption, and as the numbers approach the 1,000 mark it is probable that the two main groups are representative and provide fair contrasts.

Available figures on the other points are far from complete. Relatively few provide information on the severity of the wounds, but when they are given they show (as in Table I in Lt-Col R. L. Holt's report) that infection is more common in the extensive wounds with much tissue damage. In 161 cases it is stated that primary surgery was adequate, in at least six it was inadequate, and for the rest the matter is not mentioned. Time intervals between wounding and assessment of results were given in several reports, but we have no information about the intermediate periods between wounding, primary surgery, and assessment.

In eighty-nine men with no (0) infection, the interval between wounding and assessment averaged 4.2 days.

In thirty-one men with slight (*) infections the interval between wounding and assessment averaged 5.4 days.

In seventeen men with moderate (**) infections, the interval between wounding and assessment averaged 6.6 days.

In three men with severe (***) infections, the interval between wounding and assessment averaged 5.6 days.

These figures reveal the importance of the time factor. Presumably the severe infections were caused by more virulent organisms, but again no information is available.

The actual bacteriology of the wounds is not discussed because, when results were given, it was not always certain that any penicillin present had been neutralised.

Men with (***) infections must be regarded as complete failures and it is possible to state the causes in nine of the fifteen cases in the penicillin groups:—

2—tension not relieved by splitting of deep fascia at primary operation.

2—had tight packs in their wounds.

1—had an extensive wound with gross tissue damage.

1—had a fragment of an incendiary missile still in situ.

1—had a flank wound contaminated by a nearby colostomy.

1—had a piece of battle dress buried in the depths of a lacerated wound.

1—had a completely smashed foot with vascular gangrene of the sole.

CONCLUSION

Men who received prophylactic penicillin alone and no sulphonamides showed no higher incidence of infection.

If prophylactic penicillin is given, particularly by the parenteral route, sulphonamides are unnecessary. Indeed, in such cases they should be avoided since they are more liable to cause undesirable reactions and complications than penicillin.

INVESTIGATIONS INTO THE PROPHYLAXIS AND TREATMENT OF WOUND INFECTION

By Lt.-Col. J. C. Anderson, RAMC, Officer i/c Surgical Division, 29 *(Br.) General Hospital.*

The number of cases in several sections of this report is too small for definite conclusions to be based on them, but when added to those from other hospitals they may prove of value.

The first table shows the degree of infection present in 246 wounds treated by different methods before admission:—

TABLE I

Agents used	Total Cases	Degree of Infection							
		0	Per cent	*	Per cent	**	Per cent	***	Per cent
Parenteral and local penicillin. No sulphonamide . . .	82	61	74.4	16	19.5	4	4.9	1	1.2
Parenteral and local penicillin and oral sulphonamide . .	90	70	77.8	18	20.0	1	1.1	1	1.1
No penicillin. Oral sulphonamide . .	46	24	52.2	19	41.3	3	6.5	0	0
No penicillin. No sulphonamide . .	28	15	53.6	10	35.7	3	10.7	0	0

From the above table, it will be seen that ninety patients had received both penicillin and sulphonamide and eighty-two had received penicillin only. In the former group, eighty-eight (97.8 per cent) had no or only slight (*) infection and in the latter group, seventy-seven (93.9 per cent). The difference (3.9 per cent) is of no statistical significance, and from this series it would appear that prophylactic penicillin alone is as effective as combined penicillin and sulphonamide.

The figures in the remaining groups are too small for serious consideration, but indicate that the percentage of wounds completely free from infection drops sharply when no prophylactic penicillin

has been administered. A strict comparison cannot be made between these cases and those in previous groups as the average severity of the wounds was less.

Table II gives the results in 269 wounds treated with a variety of agents and delayed primary or secondary suture, correlated with the condition of the wound at the time of admission.

All patients who had been treated with penicillin before admission were continued on penicillin for as long as necessary afterwards, and a number who had received none before were treated with penicillin after admission.

As regards duration of treatment, the surgeons were guided by the condition of the wound when first seen and the subsequent progress of the case, but in general the methods and dosages used conformed to those recommended in the 21 Army Group Memorandum on Penicillin. It will be noted that some wounds were treated by sulphonamides, "Nuflav", sulphathiazole-proflavine powder, etc. These were applied locally and no oral sulphonamides were given to any patients after admission to hospital.

In accordance with the instructions issued in the Memorandum on Surgery No. 8, in calculating percentage successes both Grade I and II results have been included. This, however, may convey a somewhat false picture, and if the higher standard represented by Grade I is taken a truer impression of the value of penicillin is obtained—especially if one remembers that the penicillin treated groups contained a higher proportion of serious cases. These points are mentioned again in the remarks column in Table II (See next page).

Table III shows the effect of delay in primary surgery on the incidence of infection:—

TABLE III

Interval between wounding and Primary Surgery:	Total cases	Grade of Infection				Result of Suture			
		0	*	**	***	Grade I	Grade II	Grade III	per cent Success
Under 12 hours	30	28 93.3 %	1 3.3 %	1 3.3 %	0 -	15 88.2 %	2 11.8 %	0 -	100 %
12 —24 hours	74	60 81.0 %	11 14.9 %	2 2.7 %	1 1.4 %	57 81.4 %	9 12.9 %	4 5.7 %	94.3 %
24 — 48 hours	36	26 72.2 %	8 22.2 %	1 2.8 %	1 2.8 %	28 82.4 %	5 14.7 %	1 2.9 %	97.1 %
48 —72 hours	15	8 53.3 %	6 40.0 %	1 6.7 %	0 -	9 69.2 %	4 30.8 %	0 -	100 %
72 — 96 hours	14	12 85.7 %	2 14.3 %	0 -	0 -	10 71.4 %	2 14.3 %	2 14.3 %	85.7 %
Over 96 hours	22	9 41.0 %	11 50.0 %	2 9.1 %	0 -	15 78.9 %	3 15.8 %	1 5.3 %	94.7 %

The longer primary surgery is delayed the smaller is the percentage of wounds completely free from infection. The more severe the wound the earlier it is selected for operation and when this fact is

TABLE II

Agents Used	Total Cases	Grade of Infection				Result of Suture				Remarks
		o	*	**	***	Grade I	Grade II	Grade III	% Success	
Penicillin and Sulphonamide before admission. Local and in most cases Parenteral Penicillin after admission	85	67	16	1	1	71 83.5 per cent	12 14.1 per cent	2 2.4 per cent	97.6	Note high proportion of cases free from infection and the high proportion of Grade I results.
Parenteral and local penicillin only before and after admission. No Sulphonamide.	82	61	16	4	1	45 78.9 per cent	7 12.3 per cent	5 8.8 per cent	91.2	For military reasons, 25 cases had to be evacuated before final results could be assessed. The proportion of cases free from infection and giving Grade I results is still high.
Sulphonamide but no penicillin before admission. Local penicillin only after admission.	27	18	9	0	0	17 63.0 per cent	10 37.0 per cent	0 —	100.0	Proportion of cases completely free from infection and giving Grade I results is falling in absence of Penicillin.
No penicillin or sulphonamide before admission. Local penicillin only after admission.	24	15	7	2	0	17 70.8 per cent	6 25.0 per cent	1 4.2 per cent	95.8	— ditto —
Parenteral penicillin and sulphonamide before admission. Local penicillin through tubes after admission.	20	14	3	1	2	15 83.3 per cent	3 16.7 per cent	0 —	100.0	This group includes those men with gross laceration of muscle and contamination yet the proportion of Grade I results is high—considering the type and severity of the wound.
Sulphonamide before admission and local "Nuflav" afterwards	19	9	10	0	0	7 36.8 per cent	9 47.4 per cent	3 15.8 per cent	84.2	Note high incidence of infection and low proportion of Grade I healing.
Sulphonamide before admission and local sulphathiazole—1 per cent proflavine after admission.	4	0	2	2	0	1 25.0 per cent	2 50.0 per cent	1 25.0 per cent	75.0	— ditto —
Sulphonamide before admission and local sulphonamide suspended in 1 : 1000 Acriflavine Solution after admission.	8	0	6	2	0	3 37.5 per cent	3 37.5 per cent	2 25.0 per cent	75.0	— ditto —

Footnote: For military or tactical reasons a number of men had to be evacuated before the result of treatment had been determined. This accounts for occasional discrepancies in the totals in the tables.

taken into consideration it will be appreciated that the risk of infection after delay is even greater than the table would indicate. Most of these cases had prophylactic penicillin and the majority also had oral sulphonamide.

In Table IV an attempt is made to assess the best day for closing a wound.

TABLE IV

Result of Suture	Primary Suture	Delayed Primary Suture (2-7 days)						Secondary Suture 8-20 days
		2	3	4	5	6	7	
Grade I . .	34	3	31	23	19	10	4	18
Grade II . .	3	2	2	6	6	1	3	5
Grade III . .	0	0	1	2	1	1	0	1
TOTALS .	37	5	34	31	26	12	7	24

The cases closed by primary suture include an undue proportion of slight wounds. Closure of the wound by delayed primary suture on the third day after primary surgery would appear to give the best results.

In Table V the failures, *i.e.*, Grade II and Grade III cases are reviewed (See next page).

Six out of eight cases of complete failure (Grade III) were due to infection. Infection is the predominant factor in Grade II results also.

PENICILLIN ASSAY OF JOINT FLUIDS

Three assays of knee joint fluids were performed. All three patients had 100,000 units penicillin injected directly into the joint, and in addition two were receiving 15,000 units parenterally by three hourly injections.

The synovial fluid was aspirated in two cases forty-eight hours after injection and in one case ninety-six hours after injection of the penicillin into the joints. No penicillin was detected in any of the joint fluids.

CONCLUSIONS

The one factor which appears to have a marked influence on results is penicillin. As a result of clinical observation we have no hesitation in stating that the whole aspect of the surgery of trauma has been altered since its introduction.

Table V

	Infection	No cause mentioned	Gross Laceration	Healed by Granulation	Tension	Bone involved	Foreign Body
Grade II (35)	Thigh — Clinical Thigh — Clinical Back — Staph. Aureus Back - Clinical Buttock — B. Proteus Thigh — Staph. Aureus Leg — Clinical Hand — Clinical Foot, Thigh — Staph. coagulase + Forearm — Cl. Welchii: Staph. Thigh — Staph. and non-haemolytic Strept. Leg — Clinical	Back Buttock Chest wall Knee Forearm Hand Forearm Thigh	Buttock Leg Leg Thigh Arm Thigh Thigh	Loin Toe-Fract. phalanges Hand-Fract. phalanges Back Neck (fabric present)	Leg	Ankle-gross laceration	
	13	8	7	5	1	1	0
Grade III (8)	Shoulder — B. Coli Shoulder — Staph. Aureus Buttock — Cl. Welchii, B. Coli, Enterococci Arm — Clinical (fabric and metal) Hand — Cl. Welchii, Cl. Sporogenes Thigh — Staph. Aureus				Leg Leg		Leg; FB removed 10days after suture. Healed grade II thereafter.
	6	0	0	0	1	0	1

1. The onset of infection is delayed and its virulence is reduced.

2. Early surgery is still advisable but delay is no longer dangerous in most cases. It is still urgently required when gross laceration of muscle is present and particularly when a major blood vessel has been injured at the same time.

3. Since the advent of penicillin the base hospital surgeon has become an animated sewing machine. Primary or delayed primary suture is the treatment of choice in nearly all cases. From our small series of cases we believe the third day to be the best time for closure of the wound by delayed primary suture. Parenteral penicillin should be maintained till then.

4. The most efficacious method of giving penicillin is probably by parenteral injection. In cases with very severe laceration of muscle and a deep track, the instillation of penicillin solution by a tube has certain advantages over the insufflation of penicillin powder.

5. We believe that it is unnecessary to carry out routine bacteriological tests before suture. It is sufficient to rely upon clinical judgment in this matter, bacteriological investigation being reserved for cases resisting treatment and the surgical failures. In this respect one has to revise one's idea regarding the appearance of an infected wound.

Bacteriologically clean wounds may have a coating of fibrin or even a slight sero-purulent exudate which does not prejudice suture. Hyperaemia, induration, or oedema of the surrounding tissues would be criteria of infection.

6. Penicillin has made base hospital surgery easier and more within the compass of a GDO. The place for the experienced surgeons would appear to be either with the forward units or with specialised units in the hospitals at home. The work of the less experienced surgeons would require supervision.

7. It is certainly advisable to hold cases for four days after suture. In the absence of obvious complications it is safe to move many cases after that period, provided the affected part is kept at rest.

8. Twenty-two cases were allowed to heal by granulation. Despite the fact that they were nearly all slight wounds, the average time they took to heal was nineteen days. Such cases treated by excision and suture would have been healed in less than fourteen days. We believe that practically every wound, however slight, should go through the theatre for suture.

9. *One class of case is completely uninfluenced* by parenteral penicillin or any other form of internal medication. We refer to patients who have suffered damage to a considerable blood vessel which supplies a group of muscles and who have laceration of the

affected muscles. Parenteral or internal medication does not protect such individuals as the drug never reaches the damaged area. Such cases are in danger and should be held by the unit which carries out the primary surgery for at least four days, *i.e.*, until the risk of infective myositis has passed. In one month we have amputated three such limbs at a base hospital.

10. The major cause of failure is infection by penicillin-resistant organisms. Secondary causes are tension on the suture line, either due to loss of tissue or owing to excessive movement of the part. Immobilization of the affected part, after suture, even in soft tissue lesions, should be more frequently practised.

11. Other contrast agents compare very unfavourably with penicillin, but they have a place in the treatment of wounds infected with penicillin-resistant organisms. When wounds are treated by powder, such as sulphathiazole-proflavine or "Nuflav", it is better not to insufflate the wound at the time of suture but to carry out insufflation for the last time one or two days before suture.

The following officers have contributed to this investigation:—

29 (*Br*) *General Hospital*

Maj C. N. Robinson	Maj W. G. Mills	Maj H. B. Boucher
Lieut J. D. T. Jones	Capt S. T. Irwin	Capt D. H. Jenkins
Capt C. C. R. Peebles	*Maj C. E. Lumsden	*Maj S. J. De Navasquez

(*Pathologists)

74 (*Br*) *General Hospital*

Lt-Col H. B. Lee	Maj M. Backwell	Lieut O. O. Cowpe

REPORT ON WOUND SUTURE

By Lt.-Col. J. W. Bridge, RCAMC, Officer i/c Surgical Division, 21 *Canadian General Hospital.*

During the first three months of operation of this hospital surgical work was confined almost entirely to accident admissions and minor surgical cases from local static units. Three convoys of convalescent wounded yielded no cases suitable for wound study. We did, however, have under our care a group of men with self-inflicted wounds, and from a study of these cases it was felt that the concept of non-excision of "through and through" gunshot wounds was erroneous, as most of these wounds were unhealed and weeping up to periods of twenty-five to forty days following wounding. In many of these cases secondary excision was carried out before suture, and prompt healing followed. We therefore adopted the policy of early excision of this type of wound, with delayed primary suture, and found that healing occurred in approximately 95 per cent of cases within a grade I classification.

RESULTS IN 34 "T & T" GUNSHOT WOUNDS

Sixteen Cases. No primary Surgery. T & T GSWs seven to forty days old on admission.

Excision and suture, with penicillin-sulpha powder locally. Twelve cases healed within twenty-one days after suture.

Four cases delayed beyond this period due to tissue loss

75 *per cent Success.*

Eighteen Cases. Excision within one to seven days

Delayed primary or secondary suture, with penicillin-sulpha powder locally.

Seventeen cases healed within twenty-one days. One failure.

94.4 *per cent Success.*

It would appear that early excision, even when the entry and exit wounds are small as in many GSWs, promotes earlier healing. This is not generally realised.

CONDITION OF WOUNDS ON ADMISSION

The only grossly infected wounds seen in this hospital were in a group of German prisoners evacuated from captured hospitals. This group was uniformly septic, with dirty, incompletely excised

and debrided wounds, and marked pus-pocketing. Many relatively simple wounds which might have been simple suture problems if adequately excised and treated with penicillin, had resolved themselves into difficult problems of local and general sepsis, and rehabilitation appeared almost insurmountable in many cases. It is important to state that the initial treatment in all these cases was provided by German surgeons in German units.

BATTLE CASUALTIES

During the next two and a half months to March 31, 1945, this Surgical Service has been concerned with battle, mine and booby-trap casualties from around the Dunkirk area, and surgical emergencies and routine surgical cases from a rather large static garrison in Channel Ports. Opportunities of wound suture have only arisen in conjunction with the casualties from enemy mines and weapons and these have been limited in number. No convoys have been received and the only forward cases we have seen have been Canadians transferred from British hospitals in the convalescent stage. Wounds available for study have generally been of the dirty, lacerated type produced by mines and booby-traps.

WOUND SUTURES

Ninety-two patients have had delayed primary or secondary suture performed following primary excision.

1. Parenteral penicillin was given in one group and penicillin powder used at the time of suture.

2. A second group had parenteral penicillin and sulpha by mouth, with penicillin-sulphathiazole powder used locally.

3. A third group were treated with sulpha locally and orally, and received no penicillin.

4. A fourth group of four cases only had proflavine-sulphathiazole powder applied to their wounds.

The analysis is as follows:—

DELAYED PRIMARY OR SECONDARY WOUND SUTURE FOLLOWING EXCISION

Agent used	Total Cases	Grade I	Grade II	Grade III	Per cent
1. Penicillin . . .	52	39	9	4	92.3
2. Pen and sulpha . .	14	9	2	3	78.6
3. Sulpha . . .	22	14	6	2	90.9
4. Sulpha proflavine .	4	2	0	2	50.0
TOTAL . . .	92	64	17	11	—

In the first group (treated with penicillin parenterally and locally) six of the nine cases classed as Grade II were eighty-five per cent healed at fourteen days, and of course they were completely healed by twenty-one days.

Numerous small grafts were done in conjunction with wound suture and these took in accordance with the above table, and consolidated at the same time sutured wounds were healing. Most of the patients recorded in the above table had two or more wounds, and several had partial closure with a graft covering the remainder of the wound.

OPTIMUM TIME FOR SUTURE

It is our opinion that suturing after the seventh day is less likely to produce as rapidly a healing wound as suture undertaken at three or four days, and in our total series only five cases had primary surgery delayed beyond seven days. Of these, four fall into Grade II or Grade III (all on parenteral penicillin) and all showed staphylococcal or coliform contamination.

We have seen very few "gas gangrene prone" cases, and only seven of the above cases represent major compound fractures, one falling into Grade II, and another (bilateral supracondylar fractured femurs) developed severe sepsis and is as yet unhealed. Included in the above table are four penetrating knee joint cases, all healing in Grade I uneventfully.

BACTERIOLOGICAL FINDINGS

We have been unable generally to correlate bacteriological findings with wound suture results, and in the cleanly excised and penicillin treated wounds, general duty officers and surgical specialists seem to achieve equal results in those cases which fall into the category generally assigned to GDOs. (Less severe cases). The following organisms were isolated in a group of cases examined:—

Staph. Aureus	3	
Sap. Staph.	3	
Coliforms	5	
Proteus	3	
Pyocyaneus	1	(Failure to close—extensive soft tissue damage treated with grafts)
Haem. Strept.	2	
Non. path. clostridia	2	
B. welchii	2	
No growth	15	

RESULTS FOLLOWING EARLY TRANSFER FOLLOWING SUTURE

In one group of nine officer patients transferred here two days after delayed primary suture elsewhere all wounds were healed and dry within fourteen days after wounding. These were, however, minor wounds with no infection and relatively little muscle damage. In these transport seemed to have no appreciable effect.

FAILURES

Delays in healing and failure in healing in our experience seem to be due more to late suture combined with unfavourable situation and tension than to other factors.

CONCLUSION

It is regretted that the series was not larger so that more definite findings could be recorded, and we feel that no definite conclusions can be drawn from the above small series of cases, even though it would appear that penicillin has produced from 12 per cent to 25 per cent better results. But we feel also that wounds which have received the benefit of good and thorough surgery did quite well despite the giving of one or other of the various chemotherapeutic agents.

REPLY TO QUESTIONNAIRE CONTAINED IN MEMORANDUM ON SURGERY No. 8

By Lt.-Col. C. J. Cellan-Jones, RAMC, Officer i/c Surgical Division, 96 (*Br.*) *General Hospital*

The following remarks are based on experiences in four different theatres of war between 1941 and 1945.

1. MALTA, 1941—1943

Bacteriostatics available. The only agents supplied were sulphanilamide and sulphathiazole and they were administered by mouth and used as local applications. Sensitivity to these drugs caused frequent instances of persistent dermatitis, seven cases of haematuria with temporary anuria, and two cases of agranulocytosis.

Treatment of Wounds. Immediate or delayed primary suture of fifty-three wounds was attempted with slavish attention to asepsis. Success did not exceed 20 per cent and the practice was abandoned because of the frequency with which deep and spreading infections arose. Secondary suture, often as long as three months after wounding, was performed in ninety-four cases. Even in these circumstances results were poor. More than 50 per cent of the wounds broke down partially or completely.

Average Healing Period. Wounds involving soft tissues and musculature which had been excised thoroughly, according to the original policy, healed after an average period of six to nine weeks, depending on surface area and depth. Scars were disfiguring, inelastic and, in certain situations, frankly incapacitating.

Fractures. No attempt was made to close "open fractures" and, consequently, mild or even severe bone infection was seldom averted. Prolonged immobilisation in plaster was essential and a permanently reduced range of movement at neighbouring joints frequently resulted.

Wounds Involving Joints. In spite of prompt surgery, bomb fragment wounds involving the knee joint in particular were liable to be complicated by suppurative arthritis, occasionally sufficiently severe to necessitate amputation.

2. EGYPT, 1943

In this campaign also sulphonamide drugs were the only available bacteriostatics. The avoidance of "complete excision" of wounds reduced the period of healing to some extent, but climatic conditions and the longer time interval between wounding and the institution of definitive surgery were unfavourable features. The malodorous closed plaster treatment of compound fractures, with its recognised disadvantages, was adhered to. Further attempts at secondary suture of wounds met with no better fortune than in Malta.

3. ITALY, 1943—1944

In this campaign a limited supply of sulphathiazole-penicillin powder was available, but parenteral penicillin was strictly reserved for specific cases. It was not until mid-summer that compound fractures, heavily infected soft-tissue wounds, etc., could be adequately treated with the new drug. Nevertheless an immediate improvement was noticed in the condition of wounds on inspection at base hospitals. In 630 uncomplicated soft tissue wounds which came under my own supervision, 71 per cent gave Grade I and II results following local penicillin and delayed primary suture. For the first time it was found possible to avoid amputation and massive tissue resection in cases of proved anaerobic myositis. Amongst Yugo-Slavs admitted completely untreated several days after wounding, I am confident that parenteral penicillin saved many limbs. I had not sufficient confidence at this time to close compound fractures, although many opportunities presented themselves.

4. BLA, 1945

It was noted that almost all cases had been treated within a few hours after wounding. Surgical measures adopted at FSUs were thoroughly commendable and it was noted also that there was no delay in evacuation to base hospitals. The great difference from our point of view lay in the routine use of parenteral in addition to local penicillin. Admittedly many patients had also received sulpha drugs, but the dosage was small and confined to a very short period. The technique of delayed primary suture in 132 uncomplicated wounds did not differ in the slightest degree from that adopted in previous campaigns. As the table indicates, completely successful (Grade I) healing was secured in almost exactly 90 per cent of the cases and only one was relegated to "Grade III". It is interesting to note that this patient who had a five inch tangential wound of the chest wall had only received local sulphathiazole in the forward area and that, in error, he was not given parenteral penicillin here. His wound broke down completely on the sixth day.

RESULTS OF DELAYED PRIMARY SUTURE IN 132 WOUNDS

Agent used, Average dosage and operations performed	Number of wounds	Grade 1	Grade 2	Grade 3	Per cent Succes
Local and parenteral penicillin ab initio and continued in Hospital after delayed primary sutures — average dosage 500,000 units	84	79	5	0	100.0
Local penicillin at original operation — sulphonamide (5—10 gms). Parenteral penicillin in Hospital prior to and following delayed primary suture (average dosage 400 000 units).	47	40	7	0	100.0
Sulphonamide only locally and by mouth — 12 gms — delayed primary suture	1	-	-	1	-

In addition to the tabulated cases, eleven "through and through wounds" (four forearm and seven leg) complicated by open fractures of one or both bones, were treated by delayed primary suture on the fifth day. In every case "Grade 1" results were secured and this to my mind, represents the most important surgical advance directly attributable to penicillin therapy.

The following are expressions of opinion based on personal experience:—

1. The synergism between sulphathiazole and penicillin which is alleged to exist in vitro is not borne out in practice. For various reasons the sulpha drugs are not ideal diluents for penicillin powder and other diluents such as dried plasma are probably preferable.

2. Irrigation tubes are an essential part of the treatment when delayed primary suture entails leaving a large "dead space" in the tissues. The tubes are preferably made to emerge through small independent stab wounds.

3. Removal of an infected superficial or deep foreign body does not interfere with delayed primary suture so long as irrigation tubes are inserted.

4. Undercutting of wound margins should only be practiced during secondary suture and when skin-tension renders it unavoidable. Spreading infection and "tentage" are much less likely to arise if the margins are merely lifted and freshened by gauze pressure.

5. If penicillin is employed parenterally and locally, it is possible to suture wounds under somewhat greater tension than without this drug.

6. Swabbing of wounds seldom yields useful information as regards the advisability of delayed primary suture. In Italy all wounds were swabbed, and I often found that wounds alleged to be contaminated by B.coli or other resistant organisms healed without incident. On the other hand, other wounds which were described as "sterile" not infrequently broke down.

7. The administration of anti-gas-gangrene serum is sometimes followed by severe serum reactions and one might now consider abandoning its prophylactic use in favour of parenteral penicillin only.

I wish to acknowledge the help of Major T.C.F.L. Williamson and Major K.G.E. Mackenzie, Surgical Specialists, in conducting this investigation.

INVESTIGATION INTO THE PROPHYLAXIS AND TREATMENT OF WOUND INFECTIONS

By Lt.-Col. M. Fallon, RAMC, Officer i/c Surgical Division, 74 (Br.) General Hospital

The investigation of the above problems and wound healing in general has been limited in this unit by small numbers of battle casualties, unsuitable types of wounds, and changes in Divisional Officers.

The taking over in February, 1945, by the present Divisional Officer coincided with the arrival of a few convoys of lightly wounded. It was decided to close as many wounds as possible and to use a standard technique. Most of the cases had received surgical treatment, penicillin injections—in various dosages, and also had routine sulphonamide by mouth.

One was struck by the remarkable well-being of these cases and the painlessness of their wounds. No surgeon of war experience can be but impressed by the wounds which now reach base hospital level.

As a routine the wound is first inspected in the operating theatre prior to anæsthesia. Admittedly this procedure is "blind", but it eliminates the old practice of pulling off the dressings of an entire surgical convoy, seeking clean wounds—a procedure which can only lead to contamination. The secondary closure of a wound appears to have many surgical interpretations, as any discussion with surgeons will show; some state that all you have to do is to draw the skin together with a few SWG sutures; with others the most meticulous secondary trimming and undercutting is the rule. Success probably lies mid-way between these extremes. No skin edges, separated for days, can be drawn together sufficiently accurately for primary healing to follow. On the other hand indiscriminate undercutting can lead to disaster.

The technique now employed is a simple one. The wound is inspected for the first time in the operating theatre. The skin edges are cleansed with CTAB (if not available, nothing more colourful than saline is used). The gelatinised blood clot, if still present, is removed. The fat edge which seems to bulge or grow forward into

the wound is removed with scissors, flush with the skin edge. The skin edges will then be found to approximate without tension; if not an occasional touch of a sharp scalpel along the margins will loosen the edges. Any loose tags of muscle or fat are removed and the wound is frosted over with penicillin powder (5,000 units to 1 gramme sulphathiazole). Mattress SWG sutures are used for approximation. The suture line is also frosted and a *thin* layer of vaseline gauze is applied; a gauze layer is strapped on over this—this being the only dressing. Stitches are left in for a minimum of ten days.

Emphasis in this technique is placed on:—

(*a*) Minimal amount of surgical trauma:

(*b*) A simple dressing (no wound will heal satisfactorily if stifled with layers of vaseline gauze, wool or impermeable Elastoplast; a healing wound must breathe):

(*c*) A short anæsthesia—Pentothal is ideal.

Using this technique one surgeon's results in sixty-two consecutive cases (six other cases were done in this period but had to be evacuated after forty-eight hours; their wounds were then satisfactory but as their after history is not known they are not included as successes) were as follows:—

Grade I	Grade II	Grade III
(*Success*)	(*Partial Success*)	(*Failure*)
57 = (92 per cent)	3 = (5 per cent)	2 = (3 per cent)

ANALYSIS OF FAILURES

GRADE II

1. Wound over tibia inspected with view to suture, piece of clothing removed from its depths—metallic FB not found, but hole seen in tibia. Three days later this FB was removed from medullary cavity and the skin closed. Wound slow to heal but completely healed in seventeen days.

2. Officer with enormous wound 9×7 inches in right buttock, brought together under considerable tension; in twelve days the wound was well held together except for a few local areas of skin slough.

3. Should probably be in a higher category. E and E wounds in the back with a bridge of skin undermined and contused. Suture of wounds was successful but skin bridge sloughed later and was allowed to granulate.

GRADE III

1. An officer with a large E and E wound in right thigh sutured. Healing per primam. Eleven days after suture a sinus appeared in one wound which continued to discharge. On exploration a large piece of clothing was removed from its depths. Wound then healed.

2. Clean wound over deltoid—sutured—broke down six days later—cleaned up with antiseptics—second attempt was only partially successful. Complete healing by granulation in four weeks. (This case was the only one in the series where suture was carried out late.)

In an analysis of the above series the Grade I cases averaged six days between wounding and final closure. The Grades II and III cases averaged nine days.

To summarise our experience:—

(*a*) The sooner the skin is closed over a clean surgically treated war wound the better. The aim should be to do this at the first general hospital.

(*b*) The decision to close a wound should be made on clinical grounds alone—on the appearance of the wound. To take swabs and await bacteriological findings wastes time that is all important.

(*c*) At the time of suture any FB still in situ should not be looked for; otherwise the skin suture may be unsuccessful.

(*d*) There is no objection to trimming (or excision) of a previously untreated wound and then suture—provided the wound looks clean.

(*e*) Sutures for finger or foot wounds should be avoided. Although clean there is always œdema.

(*f*) It is better to approximate the skin under tension than to leave a wide gap to granulate. There is no objection to the relief of this tension by use of the recognised methods. We have had no experience of lateral incisions or flaps.

(*g*) Fractures at the base of a wound do not preclude suture, provided loose and detached fragments are removed.

(*h*) There is no objection to sutures of large E and E wounds of thigh with deep fascia involvement.

(*i*) Penicillin and chemotherapy locally have no obvious specific action (apart from bacteriostatic) on the rate of wound healing.

(*j*) There is no necessity to continue the use of either *after* suture unless in the doubtful case where a change of mind would be justifiable.

These observations are recorded to illustrate that the success in war surgery to-day is attained forward and is already established—thanks to good surgery, penicillin and sulphonamide—before the patient reaches a base hospital.

Here we add to that success by closure of the skin; further penicillin and chemotherapy appears to be unnecessary.

In a new series *all* local preparations (penicillin powder, etc.) at the time of suture are being dispensed with. The results in a small group of fourteen cases are as follows:—

Grade I	Grade II	Grade III
(*Success*)	(*Partial Success*)	(*Failures*)
12=(86 per cent)	2=(14 per cent)	Nil

We have no experience in treating (by suture) the inflamed or septic wound nor have we experience of the effects of other preparations (*e.g.* Marfinil, Proflavine, etc).

REPORT ON PENICILLIN INVESTIGATION

By Lt.-Col. R. S. Handley, RAMC, Officer i/c Surgical Division, 101 *(Br.) General Hospital*

It has not been found possible to collect sufficient material for a statistical answer to Question A. Many cases were received in which the investigation had been properly initiated but had been spoiled by the giving of sulphonamides during evacuation. There is no doubt in my mind that there is no difference between wounds treated with penicillin only and with penicillin and sulphonamides.

The material collected under Question B consists of sixty-four cases, with 104 wounds. The small number of wounds, when divided up into the numerous methods of treating them, does not provide statistically significant evidence. Analysis of the cases yields the following table:—

Agent	Total cases	Total wounds	Healing		
			Grade I	Grade II	Grade III
Local penicillin only	12	13	11	1	1
Local and systemic penicillin	22	46	33	9	4
Systemic penicillin only	5	10	10	—	—
"Nuflav" only	4	5	2	1	2
Local penicillin and systemic sulphonamide	2	2	2	—	—
Local penicillin, systemic penicillin, and systemic sulphonamide	7	14	13	—	1
Systemic penicillin and systemic suplhonamide	7	9	6	1	2
Nil	5	5	4	—	1
Totals	64	104	81	12	11

This table shows that only 10 per cent of the wounds sutured were classed as failures; many of the failures were in fact partial failures only. Total failure was rare. The table supports, with admittedly slender evidence, the clinical impression that "Nuflav" was much inferior to penicillin and sulphathiazole powder. Locally applied penicillin appears to be as effective as systemic penicillin treatment,

though this finding is subject to the fallacy that medical officers tended to put the worse wounds on systemic as well as local penicillin.

No cases in this series were skin grafted.

With three exceptions, the series consisted of flesh wounds varying from 1 to 5 inches in length. In three instances a foreign body was known to be in situ but all three healed within ten days. No wound was sewn up at the same operation as for removal of a foreign body. The wounds were further analysed for site and speed of healing and the following table produced:—

Region of Wound	Total cases	Healing Grade I	Grade II	Grade III
Arm	17	17	—	—
Back	17	9	4	4
Thorax	1	1	—	—
Thigh	31	22	4	5
Leg	32	28	4	—
Neck	3	3	—	—
Abdominal Wall	1	1	—	—

Few swabs were taken from wounds. The clinical state of the wound is a better guide to treatment than the laboratory findings. The following table compiled from a somewhat small number illustrates this.

RESULT	Total cases	Clinical degree of infection 0	*	**
Success	17	10	7	0
Failure	9	2	6	1

I do not think that swabs for bacteriological examination assist in prognosis or treatment. They should only be used in cases of failure.

Failure of a wound to heal at the first suture is not a contra-indication to a second attempt which is often successful.

The majority of the wounds were closed without either undercutting or excision of the edges. Excision of the wounds and suture was found to be quite safe and left a tidier scar than mere pulling together of the edges, but the small number treated by excision showed no difference as regards success in or speed of healing.

Wounds seen in the present campaign are much cleaner than those seen in the BEF or in the ME. I believe that penicillin must receive most of the credit for this state of affairs; the shorter and speedier journeys which the wounded now make before receiving full surgical attention are an important supplement in this respect.

The information on which this report is based has been largely supplied by Capt. (Miss) Hewitt, R.A.M.C., Capt. (Miss) Graham, R.A.M.C. and Capt. Mosscrop, R.A.M.C.

CONSOLIDATED RETURN ON WAR WOUND INVESTIGATION

By Lt.-Col. R. L. Holt, RAMC, Officer i/c Surgical Division, 30 (Br.) General Hospital

1. *Question:* "Is there any advantage gained by using oral sulphonamide in addition to penicillin as a prophylactic against wound infection?"

Answer: The following table gives a summary of the results of wound swabs taken from unselected cases. The cases have been graded according to the severity of the wound into three groups:—

(*A*) Wounds involving skin and subcutaneous tissues.

(*B*) Wounds involving muscle, *e.g.*, perforating and penetrating wounds of limbs.

(*C*) Extensive wounds causing extensive muscle damage and including cases of compound fracture of long bones.

All the cases included received adequate preliminary surgery.

TABLE I

Therapeutic agent	Severity of wound	No. of wounds swabbed	Sterile	Infected
Penicillin only	A	1	1	—
	B	44	39	5
	C	11	6	5
Penicillin and oral sulphonamide	A	2	2	—
	B	30	28	2
	C	12	8	4

Further information may be obtained from Table II which summarizes the results of delayed primary and secondary sutures according to the chemotherapy employed before suturing.

TABLE II

Agent employed	Days between wounding and suture	Total Cases	Healing Grade I	Healing Grade II	Healing Grade III	Per cent Success
Penicillin	1 — 7	136	127	2	7	94.8
	7 — 14	38	34	3	1	97.4
Penicillin and oral sulphonamide	1 — 7	86	80	3	3	96.5
	7 — 14	30	29	1	—	100.0

Care must be used in interpreting this table since it does not take into account the post-operative chemotherapy which may in some cases have affected the grade of healing achieved.

Taken together Tables I and II suggest that penicillin plus oral sulphonamide is slightly more effective than penicillin alone.

2. *Question:* Are there any significant differences to be noted in the wounds seen in the present campaign as compared with those of other campaigns?

Answer: The most striking difference between the wounds seen in the present campaign and similar wounds seen in Egypt is the almost total absence of gross infection of the wounds in the present campaign. In Egypt, the cases which had received adequate surgery and sulphonamide therapy frequently compared favourably with those seen here; but, on the other hand, there were a very large number of cases of infected wounds in some of which infection was severe. On looking back it is evident that many opportunities of early healing were missed by failure to suture the clean cases early.

It is suggested that the factors which account for the differences in the wounds seen in the two theatres of war are:—

(*a*) *Condition of the patient's skin:* In Egypt, lack of water, caking of sweat and dust on the skin, and a shortage of water for cleansing purposes in surgical units contributed towards infection.

(*b*) *Collection of Casualties:* On the whole the casualty reached the surgical centre much later in Egypt than is the case in BLA.

(*c*) *Surgery:* The casualty in BLA almost invariably receives adequate surgery and chemotherapy within twenty-four hours and within the next day or two he reaches a hospital in which his treatment can be completed.

(*d*) *Penicillin:* This undoubtedly has helped but only to a slight extent since, if a wound receives early surgical treatment, sulphonamide gives results almost equal to those of penicillin.

There has been a very noticeable difference in the wounds of PW and British soldiers in this campaign. In the former group the majority of wounds have been grossly infected, and were similar in appearance to those seen frequently in Egypt amongst British soldiers whose wounds had been untreated for several days.

3. *Question:* What are the relative values of penicillin and other contrast agents employed as an aid to early closure of wounds?

Answer:

(*a*) *Primary Suture:* In order to obtain some information on this point, a series of wounds unselected in severity were closed by primary suture after insufflation of sulphonamide or penicillin powder. The results are summarized in Table III.

TABLE III

RESULTS OF PRIMARY SUTURE OF WOUNDS

Degree of severity of wound	Total Cases	Sulphonamides only			Penicillin only		
		Healing			Healing		
		Grade I	Grade II	Grade III	Grade I	Grade II	Grade III
A	42	19	—	1	21	1	—
B	43	17	1	—	23	—	2
C	1	—	—	—	1	—	—
Totals	86	36	1	1	45	1	2

These cases were operated on by Major R. G. Taylor and myself. They are too few to be conclusive but they suggest that in wounds of minor and moderate severity, there is little to choose between penicillin and sulphonamide as a local application to wounds submitted to primary suture.

(*b*) *Delayed Primary Suture:* The success of a delayed primary suture depends in large measure on obtaining a clean wound to suture. The following table (IV) summarizes the results obtained from wound swabs taken from an unselected group of wounds all of which had been previously treated by surgical toilet or excision and, in addition, had been treated by penicillin or sulphonamide or a combination of the two. In each case the wound swab was taken within seven days of wounding, usually between the fourth and the seventh day. In a large percentage of cases which are shown as having received sulphonamide orally or penicillin parenterally this treatment had been discontinued for several days before the wound swab was taken.

RESULTS OF WOUND SWABS TAKEN WITHIN SEVEN DAYS OF WOUNDING

TABLE IV

Agent Used	No. of Cases	No. of wounds swabbed	No. of wounds sterile	No. of infected wounds
Sulphonamide only	22	23	22	1 Staph. Coag.—
Penicillin-sulfa powder locally	5	6	4	2 Staph. coag.—Diphtheroids
Penicillin-sulfa powder locally and sulphonamide orally	3	3	3	
Penicillin-sulfa powder locally and penicillin parenterally	40	48	41	7 Staph. coag. + 3 wounds. Staph. coag. — 1wound. B. Pyocyaneus 2 wounds. Clostridia 1 wound.
Penicillin-sulfa powder, Penicillin parenterally, and sulphonamide orally	32	41	36	5 Staph. coag. + 1 wound. Staph. coag. — 1 wound. Non.Haem.Strep. 1 wound Diphtheroids 1 wound. B.Coli and Pyocyaneus 1 wound.
None used, or nil recorded	12	12	12	
Totals	114	133	118	15

This table gives some idea of the high percentage of clean wounds arriving in base hospitals from forward units. The true figure is higher than that shown since in cases with multiple wounds the wounds chosen for swabbing were those considered most likely to be infected. The largest groups of infected cases occurred in those patients receiving penicillin, but it is only fair to point out that these groups contained a higher proportion of severe wounds than the other groups.

These results of wound swabs are supported by the results of wound suture. The following tables V and VI group the results of delayed primary suture according to the form of chemotherapy employed before and after suture respectively.

RESULTS OF DELAYED PRIMARY SUTURE ACCORDING TO PREOPERATIVE CHEMOTHERAPY

TABLE V

Agent used	No. of wounds	Healing Grade I	Healing Grade II	Healing Grade III	Per cent Success
Sulphonamide only	37	33	2	2	94.6
Pen-sulfa powder locally	32	32	—	—	100.0
Pen-sulfa powder locally and sulphonamide orally	14	14	—	—	100.0
Pen-sulfa powder locally and penicillin parenterally	104	95	2	7	93.0
Pen-sulfa powder locally. Penicillin parenterally and sulphonamide orally	72	66	3	3	95.8
Totals	259	240	7	12	95.4

RESULTS OF DELAYED PRIMARY SUTURE ACCORDING TO POST-OPERATIVE CHEMOTHERAPY

TABLE VI

Agent used	No. of wounds	Healing Grade I	Healing Grade II	Healing Grade III	Per cent Success
Sulphonamide only	17	13	1	3	82
Pen-sulfa powder locally	195	184	5	6	97
Pen-sulfa powder locally and penicillin parenterally	89	84	2	3	97
Sulphonamide orally and Pen-sulfa powder locally	14	14	—	—	100
Totals	315	295	8	12	96

No clear-cut conclusion can be drawn from these tables but it would again appear that penicillin is slightly more effective than sulphonamide, and that a combination of penicillin and sulphonamide given orally is more effective than either penicillin or sulphonamide alone.

4. *Question:* Do wounded men receiving sulpha drugs and no penicillin show a higher incidence of infection than those receiving penicillin?

Answer: No—providing the wounds have received adequate surgical treatment.

The appearance of a wound three or four days after excision and the application of sulphonamide powder is sometimes rather misleading. There is frequently a marked cellular reaction on the part of the tissues in the wound resulting in an exudate containing pus cells and some induration of the subcutaneous fat. This gives the impression of a mild degree of infection but wound swabs show the wound is sterile and, if suture is performed, healing is uneventful. In contrast the wound treated by penicillin—particularly parenteral penicillin—shows a complete absence of reaction.

5. *Question:* Are there any variations in the rate of healing dependent on an increasing interval between wounding and operation?

Answer: No. From the notes on cases admitted here, it is impossible to contrast these cases according to the Table suggested. The majority of cases coming up for suture after fourteen days and many earlier than that have received a variety of drugs and dressings. The following table is inserted summarizing the results of suture of wounds—excluding primary suture—irrespective of severity or chemotherapy.

This should occasion no surprise since the later wound is almost invariably cleared of infection before suture is attempted and some of the factors tending to cause failure, *e.g.*, tentage and suppuration round FBs, are less likely to occur in the later groups of cases.

TABLE VII

Interval between wounding and suture	Total Cases	Healing			Per cent Success
		Grade I	Grade II	Grade III	
1 — 7 Days	315	295	8	12	96.0
8 — 14 Days	83	75	5	3	96.0
over 14 Days	13	12	1	—	100.0

6. *Question:* Are the results influenced by the skill of the individual surgeon?

Answer: See the following table:—

TABLE VIII

Surgeon	Severity of wound	Healing		
		Grade I	Grade II	Grade III
A	A	15	—	—
	B	89	1	1
	C	10	1	2
B	A	9	—	—
	B	35	3	1
	C	11	1	2
C	A	8	—	—
	B	17	—	3
	C	—	—	—
D	A	3	—	—
	B	37	—	1
	C	4	1	—
E	A	8	—	—
	B	29	—	1
	C	4	1	—
F	A	—	—	—
	B	8	—	—
	C	1	—	1
G	A	25	—	—
	B	41	—	—
	C	7	1	4

The first three surgeons have had more experience than the other four but the results are very even.

7. *Question:* Is the routine swabbing of wounds of any value?

Answer: The laboratory reports on wound swabs have throughout the investigation confirmed the impressions gained from a careful clinical examination of the wounds. The swab taken from a wound which looked clean was reported by the laboratory to be sterile and the wound which looked moist or dirty was found to be infected. The following table is a summary of the laboratory findings on wound swabs from unselected cases which had previously had some form of wound toilet carried out. In cases with multiple wounds the wounds which clinically were more likely to be infected were selected for swabbing.

TABLE IX

Agent used	Days between wounding and swabbing	No. of wounds	Sterile	Infected
Sulphonamide only	1 — 7	23	22	1 Staph.Coag —
	over 7	2	2	
Penicillin-sulpha powder only	1 — 7	6	4	2 Staph.Coag — 1 wound Diphtheroids 1 wound
Pen. sulpha powder locally and oral sulphonamide	1 — 7	3	3	—
Penicillin powder locally and penicillin intramuscularly	1 — 7	48	41	7 Staph.Coag + 3 wounds Staph.Coag — 1 wound Clostridia 1 wound B.Pyocyaneus 2 wounds
	over 7	10	7	3 B.Proteus and Pyocyaneus 1 wound Clostridia 2 wounds
Pen. sulpha powder locally. Penicillin intramusculary and Sulphonamide orally	1 — 7	41	36	5 Staph.Coag + 1 wound Staph.Coag — 1 wound Non.Haem.Strept.1 wound Diphtheroids 1 wound Pyocyaneus and B.Coli 1 wound
	over 7	18	8	10 Staph.Coag — 3 wounds Staph.Coag + 1 wound B.Pyocyaneus 1 wound B. Pyocyaneus and Clostridia 1 wound B.Proteus 2 wounds Staph.Coag + and B.Proteus 1 wound Clostridia 1 wound
Nil recorded	1 — 7	12	12	—
Totals	1 — 7	133	118	15 (11 %)
	over 7	30	17	13 (43 %)

This table shows the low incidence of infection, 11 per cent, in wounds treated surgically and swabbed within seven days of wounding. Of this 11 per cent half the wounds were infected with non-pathogenic organisms. The incidence of infection is, as might be expected, much higher in the later group of wounds. Hæmolytic streptococci were notably absent (but were found in other cases in which the wounds had not been excised). The commonest infecting organisms were the gram negative bacilli—Pyocyaneus, Proteus and Coli.

It is interesting to follow the progress of the wounds found to be infected when swabbed at the time of suturing.

(*a*) Staph Coag— Four wounds—all healed Grade I

(*b*) Staph Coag+ Four wounds—three healed Grade I

One failure which was due to deep suppuration round a retained FB and clothing. Wound healed initially and then broke down, discharging thin pus containing clostridia and non-hæmolytic streptococci.

(*c*) Ps. Pyocyaneus, Coli, etc—five wounds with two failures due to infection.

(*d*) Diphtheroids, Clostridia, non-hæmolytic streptococci—healed.

The laboratory findings were most useful in two groups of cases: —

(*a*) Delayed primary sutures in which Staphylococci Coag.+ were found. Penicillin was given parenterally with good results.

(*b*) Those cases in which suture for some reason or other was delayed over seven days. In these cases, treatment was instituted to clear up the infection disclosed and, as a result, suture was more successful than in the delayed primary suture series.

It would be a mistake to limit the bacteriological investigation of wounds to the failures. Routine swabbing and culture of all wounds is unnecessary but it is advisable to swab all wounds which: —

(*a*) Show any signs of infection.

(*b*) Have not been sutured within seven days of wounding.

The information obtained from the laboratory in these cases enables the surgeon to carry out the specific treatment indicated and infection as a cause of failure can be almost totally eliminated.

BACTERIOLOGICAL ASPECTS

Major C. E. Lumsden, Pathologist, 30 (Br.) General Hospital, has provided the following comments on the bacteriological aspects.

1. A very high proportion of the wound swabs examined during the past three months have yielded sterile cultures or growths of insignificant contaminants only.

2. In most cases where pathogenic micro-organisms have been isolated, this has been in accordance with clinical expectation—

i.e., the wound was clinically infected. Only rarely have the bacteriological findings given warning of impending breakdown in a wound; more frequently, where scanty pathogens were isolated from the original swab I understand that healing has occurred uneventfully following the primary treatment with penicillin-sulphonamide powder and suture.

3. Accordingly, it is my impression on the small number of swabs examined (just over 300) that routine bacteriology of these war wounds encountered at this place in the line of evacuation *does not yield any considerable dividend of clinical advantage* in the early stages.

4. Where clinical breakdown occurs, it is my present opinion that bacteriological examination should be made:

(*a*) To determine whether bacterial infection is responsible for, or contributory to, this breakdown:

(*b*) To determine the nature of the organism present as a guide to the proper antibacterial agent to be used in treatment.

Most of the breakdowns have been due to penicillin-resistant *Staphylococcus pyogenes*, or to the gram negative bacillary group, particularly *Ps. Pyocyanea.*

Ps. Pyocyanea has taken a high place in the list of pathogenic organisms isolated, and in all of these cases penicillin appears to have been applied at more forward medical units.

In this hospital we have found *Ps. Pyocyanea* on a few occasions as a contaminant in penicillin solutions (which had been used as a spray for throats or for dermatological treatment) returned from the wards —and this led to a renewed campaign for aseptic technique in the handling of penicillin in all departments! Having regard to the difficulties in forward units it is possible *Pyocyaneus* may be introduced into the wounds in some cases by the use of penicillin-sulphathiazole powders which have not been prepared and used with strict aseptic technique.*

FAILURES

In over 400 wounds sutured for which full records are available, only fifteen were unhealed by the twenty-first day after suture. The cause of failure in all except three was a technical fault. The causes were:

(*a*) Suppuration round retained foreign material—four cases.

(*b*) Tentage—three cases of which only one was a complete failure, the other two having a small persistent sinus towards the centre of the wound.

*Ed. Footnote. Until March, 1945, when this investigation ceased all penicillin powders used by Forward Units—except for relatively small amounts prepared in the actual units—were prepared in No. 3 Mob. Bact. Lab. under conditions devised and controlled by Maj K. E. A. Hughes. Each batch was assayed and tested for sterility before issue, but it is poss.ble that contamination may have occurred afterwards.

(*c*) Tension—four cases.
This is a more likely cause of Grade II than Grade III healing. Most of these failures were due to removing sutures too early or to beginning vigorous physiotherapy too soon. The wounds were not infected, were re-sutured and healed well later.

(*d*) Infection—three cases due to persistence of Ps. Pyocyaneus. One case due to Staph. Coag.+. (N.B.—This wound was not swabbed at operation.)

Tension and infection were the commonest causes of delayed healing (Grade II). Frequently the infection was secondary to the effects of tension. More rarely infection was present at the time of suture and caused some moistness of the wound. Staphylococcus pyogenes was the organism most frequently encountered and the infection almost invariably subsided under parenteral penicillin treatment.

Results of wounds involving fracture of long bones:

Results of suture of wounds associated with compound fractures of long bones and scapula (hand and foot excluded). The following table is added for interest:—

No. of Cases	HEALING Grade I	Grade II	Grade III	Per cent Success
42	34	4	4	90

Only one of the failures was complete and this was due to tentage in a wound involving the scapula.

GENERAL COMMENT

This report, in its present form, is liable to give the reader a totally erroneous impression of the value of chemotherapeutic agents in preventing or clearing up wound infection. Clinical observation and laboratory examination have shown that only about 5 per cent of wounds treated by surgical toilet and chemotherapy are infected by pathogenic organisms within seven days of wounding. But, if surgical toilet is not carried out, the rate of infection is probably higher than 50 per cent in spite of penicillin or sulphonamide.

It has been unusual in this campaign for a base hospital to receive men with wounds two or three days' old which have not been treated by some form of wound excision. But, recently, this hospital received a convoy of men wounded during the Rhine crossing and it was not surprising to find that a large number of the less severe wounds had received no surgical treatment. There were no cases of gross infection amongst them but almost all were infected, in spite of penicillin and sulphonamide treatment. Early surgical treatment remains the most important single factor in preventing wound infection.

The cases on which this report is based have been under the care of Lt. Col. R. L. Holt, Majors R. G. Taylor, K. A. Moore, P. H. Newman, S. H. Harrison, and Captains A. C. Kanaar and J. B. Jack.

REPORT ON PENICILLIN INVESTIGATION

By Lt.-Col. E. A. Jack, RAMC, Officer i/c Surgical Division, No. 8 (Br.) General Hospital

This report is rendered on conclusion of the investigations outlined in Memorandum on Surgery No. 8. An interim report on Penicillin Therapy was rendered as Appendix "G" to the Quarterly Report of the Surgical Division, October–December, 1944. As stated in that report, the original investigation into the comparable effects of local penicillin and a local contrast agent was abandoned, and instead, an attempt has been made to compare the effects of penicillin administered parenterally with local applications. This investigation has not been as fruitful as was hoped when it was started. The comparatively static and well organised lines of evacuation that existed during the first quarter of the year enabled the administration of parenteral penicillin as a prophylactic to become almost routine even for the lightly wounded, with the result that the cases available for local application only have been very few.

Cases reported in the interim report have been included in the figures quoted in this report. The standards of assessment are those suggested, and when the necessary information is available the questions are dealt with in the order given.

SUMMARY OF ALL CASES

	Total Cases	Grade I	Grade II	Grade III	% Success
Parenteral Penicillin	300	251	32	17	94.33
Local Penicillin	85	71	11	3	96.57
Total Cases	385	322	43	20	94.81

The superiority of local applications is apparent rather than real as the wounds in the two groups have not been strictly comparable. Those treated with local applications have been the minor wounds for which it was considered unnecessary to administer penicillin in the forward areas, whilst those given parenteral penicillin included all wounds for which parenteral penicillin had already been started prior to admission to the hospital. It was the policy to attempt early closure on all wounds regardless of apparent infection or bacteriological findings, and the latter group naturally includes many severe and contaminated wounds.

1. *Condition of Wounds.* Comment on the phased improvement in the general state of wounds since the beginning of the war corresponding with the organised prophylactic administration of the sulphonamides followed by penicillin, was made in the interim report. There is no doubt that the wounds arriving in a forward base hospital in this campaign have been far cleaner, and the patients in much better general condition, than in the campaigns in the Middle East, or in France in 1940. That prophylactic penicillin is in very large measure responsible for that improvement is certain. A small group of cases was received from the Ardennes salient having received no chemotherapy and all of these had an area of cellulitis surrounding their infected wounds, reminiscent of earlier days. But it must also be recognised that the facilities for early operation and rapid evacuation over relatively short distances, and the good general condition of the men prior to wounding—conditions which have prevailed during the present campaign—have also played their part. Furthermore, blood transfusions not only resuscitate shocked patients but also revitalise anoxic tissues, and possibly the widespread use of blood transfusion in large quantities has not received sufficient credit for the part it has played in bringing about the improvement.

The terrain of France and Flanders was noted for its pathogenic anaerobes, following the experiences of the last war, and gas gangrene was expected to be far more prevalent than it was in the sterile soil of the Middle East. During the last six months, eleven cases of gas gangrene have occurred in this hospital amongst 4,032 casualties. No case has died of the infection and only three required amputation of the limb. The infection has been slow in developing and of a low virulence in all but one. This fact may render the figures unreliable, in that the infection may have developed later in cases evacuated to UK within a few days of wounding.

A number of "gas gangrene prone" cases have been seen in which a mass of ischæmic muscle has presented a grey putty-like colour and consistency, without any gross infection, and excision of this mass has rapidly produced a clean wound in which suture has been possible within a few days.

In this connection the case of 14204724, Pte. Nixon, 1st Glasgow Highlanders (reported in Quarterly Report) is worth mentioning. He was subjected to secondary suture on the sixth day after wounding, having sustained injury to the posterior tibial vessels. A five days course of parenteral penicillin was given, ending on the third post operative day, and he developed gas gangrene seven days after suture—Cl. welchii, B. proteus and gram positive cocci were grown from his wound.

It is not possible to comment, with any justice, on open bone or joint injuries as the majority of these have been evacuated without interference in this hospital.

2. *The incidence of infection in cases receiving sulphonamide and cases receiving no sulphonamide:*

	Total Cases	Infection			
		o	*	**	***
Sulphonamide	94	39	44	9	2
No Sulphonamide	193	75	99	18	1

These figures show very similar results in the two groups, and it is impossible to draw any conclusions from them. It is the general consensus amongst the surgeons of this hospital that adequate regular dosage with penicillin alone gives maximum protection and that nothing further is gained by adding sulphonamides. They will not go so far as to deny any effect by sulphonamide in the absence of penicillin.

3. *Effects of interval between wounding and healing, with degree of infection:*

Wound-Operation Interval	Total Cases	Infection				Healing		
		o	*	**	***	Grade I	Grade II	Grade III
1 — 3 days	49	24	22	3	0	45	3	1
4 — 6 days	108	41	55	11	1	88	10	10
7 — 9 days	51	15	28	8	0	42	9	0
10 — 20 days	22	3	18	1	0	17	4	1

It was the policy to close all wounds at the earliest opportunity irrespective of their apparent infection (within reason). The majority of fresh wounds, owing to evacuation circumstances, fall into the 4–6 day group and include a number of cases with bone injury.

The cases in the later groups were delayed for various reasons and it will be noted that they contain a relatively higher proportion of partial breakdowns due to separation of the skin edges.

4. *The necessity for excision or non-excision* depends entirely on the nature of the wounds, the treatment carried out in forward areas, and the wound operation interval. A wound adequately trimmed at the CCS requires no further excision up to the fifth or sixth day. In older wounds new epithelium growing over granulations should always be excised back to full thickness skin. Partial breakdown is frequent if this is not done.

5. *Tension in the wound*, especially over subcutaneous bone, or tenting over a cavity are common causes of breakdown (see analysis of failures). Defects over the subcutaneous border of the tibia have been successfully closed in three cases by the use of a rotation flap from the calf with immediate Thiersch grafting of the posterior defect. It is important that bared bone or tendon is covered at the earliest opportunity by full thickness skin and that there is no tension in the suture line.

6. *The effects of removing a foreign body at the time of suture.* Many cases have had immediate suture performed after the removal of an FB, with successful healing. Those cases in which an abscess cavity has been found about an FB have been left open for two or three days after drainage, before suturing.

7. *Results are undoubtedly influenced by the skill of the surgeon* and the best results are only obtained by meticulous attention to details of technique, and by the exercise of judgement, as shown by the following figures:—

	Total Cases	Grade I	Grade II	Grade III	% Success
Surgeon A	68	59	8	1	98.53
Surgeon B	100	82	10	8	92.00

8. *Only a small number of cases have been received with stitches still in sutured wounds.*

No ill effects appear to have resulted. It has been the routine to dress all cases operated on in this hospital on the fifth day after suture, and failure or partial breakdown, if it was going to occur, has always been evident by then.

There seems to be little objection to evacuating a case on the fifth day after suture provided the wound looks healthy and the tissues are sufficiently immobilised to prevent damage by movement on a stretcher. A wound of the buttock or back is obviously unsuitable.

9. *Comparative rates of healing in sutured and unsutured wounds.* No definite figures are available. At first, however, many cases with multiple wounds had suture performed on the larger wounds and the trivial wounds left to granulate. These small wounds were always the last to heal and often delayed the patient's discharge when his larger wounds were healed. Six weeks was a usual prognosis for an average wound left to heal by granulation. Two to three weeks in hospital is the routine now. Suture is carried out on even the trivial wounds where there are skin edges to bring together.

10. *Laboratory Findings.* In the early stages of this investigation an attempt was made to carry out routine bacteriological examination of all wounds before suture. The bacteriological findings, however, did not appear to have any constant relationship

to the end results of suture. The examination increased the work, both of busy wards and a busy laboratory, very greatly, made it necessary to expose the wound prior to operation, and delayed suture in many cases. It was abandoned for these reasons, and subsequently wounds were examined in the operating theatre and suture carried out immediately if the clinical appearance seemed to be satisfactory. Clinical judgment has been a far more reliable guide than any laboratory culture. Only cases which failed to heal have been investigated for organisms.

11. *Analysis of Failures.* Thirty-seven Grade II and III results out of 229 cases have been investigated for causes of failure. They are analysed below for the situation, nature and condition of their wounds prior to operation and the bacteriology and predisposing causes after breakdown had occurred.

A. SITUATION OF WOUND.

Situation of Wound		Total Cases	Result		
			I	II	III
Lower extremity	Buttock	17	16	1	0
	Thigh	64	55	6	3
	Leg	56	48	5	3
	Foot	7	3	2	2
Upper extremity	Shoulder	11	8	3	0
	Arm	17	16	1	0
	Forearm	19	17	2	0
	Hand	14	7	4	3
Head and Neck		5	5	0	0
Trunk		19	17	1	1
	Totals	229	192	25	12

B. TISSUES INVOLVED.

Tissues Involved	Total Cases	Result		
		I	II	III
Skin and Fascia	89	85	4	0
Skin, Fascia and Muscle	93	78	9	6
Skin, Fascia, Muscle and Bone	47	29	12	6
Totals	229	192	25	12

C. SIZE OF WOUND.

Size of Wound	Total Cases	Result I	Result II	Result III
O —2 inches	88	82	5	1
2 — 4 inches	94	80	8	6
over 4 inches	47	30	12	5
Totals	229	192	25	12

D. CONDITION OF WOUND — ASSESSMENT OF INFECTION

Degree of Infection	Total Cases	Result I	Result II	Result III
Infection o	83	73	9	1
Infection *	112	104	11	7
Infection **	23	15	5	3
Infection ***	1	0	0	1

Wounds of the hand and foot seem to be particularly unsuccessful, possibly due to the unyielding nature of the skin, the difficulty of complete wound toilet, and the frequency of tension after suturing. The size of the wound and the state of infection have a natural relationship to the results. The tissues involved have a marked effect on the healing, and the incidence of breakdown in cases with bone damage was twice as high as in those with only muscle involvement.

With this fact in view the individual cases are analysed in two groups—those with bone damage and those without. (See next Page).

The first group were nearly all relatively clean wounds when suture was undertaken. The administration of penicillin was by the parenteral route in all the bone cases, and the standard dosage was used. It is seen that the failures in this group were far more frequently attributed to infection, and that the persistance of pathogenic penicillin-sensitive organisms was much commoner than in the soft tissue injuries.

In the latter group a larger number of the wounds were clinically dirty at the time of suturing and yet the bacteriological examination showed the persistance of pathogens in only few instances. In the one case in which a retained FB was noted as a factor—penicillin-sensitive pathogens persisted.

The following surgeons participated in the investigation:-

Lt.-Col. E. A. JACK
Major T. J. BROWNLEE
Major G. QVIST
Capt. E. N. BROCKWAY

18 GRADE II AND III CASES WITH BONE DAMAGE.

Nature of Wound	Infection before Suture	Tension	Cavity	Retained F. B.	Result	Bacteriology
4" transv. wrist	o	+	—	—	III	B.coli:Coag. + ve. staph.
5" vertical leg	+	+	+	—	III	Cl.Welchii; B. proteus; Gram + cocci.
3" T. and T. Thigh	+ +	—	+ +	+	III	B.Coli: Haem.strept. (sensitive).
2" amp. stump finger	—	—			III	Coag + ve. staph. (resistant).
5" amp. across knuckles	+	+	—	—	III	Not done,
3" transv. shin	+	+	—	—	III	Coag. — ve. staph.
3" transv. below knee	o	+ +	—	—	II	B. coli.
2" oblique wrist	o	—	—	—	II	Coag.—ve. staph.
3" transv. Hip	o	—	—	—	II	Haem.strept (sensitive): B. subtilis.
2" palm hand	+	—	—	+	II	Coag.—ve. staph. (sensitive).
6" amp. knee	o	+	—	—	II	B.Coli: Non-haem.strept.
2" palm hand	o	—	—	—	II	B.Coli: Coag + ve.staph.
5" vertical arm	o	—	—	—	II	Coag + ve. staph. (resiatant).
5" Amp. shoulder	+ +	+	+	—	II	B. Coli: Non-haem.strept (sensitive).
5" vertical forearm	+	+	—	—	II	Ps. pyocyaneus.
4" vertical forearm	+	+	—	—	II	Ps. pyocyaneus.
3" transv. shin	o	+ +	—	+	II	Not done.
3" oblique scapula	—	—	—	—	II	B. coli.

19 GRADE II AND III CASES—NO BONE DAMAGE.

Nature of Wound	Infection before Suture	Tension	Cavity	Retained F. B.	Result	Bacteriology
2" vertical thigh	—	—	—	—	III	B. Coli.
2" T. and T. Thigh	—	—	—	—	III	B. Coli.
2" transv. ankle	+ + +	+	—	—	III	Haem.strept. Clostridia.
6" ankle and foot	+	+	—	—	III	Not done.
4" oblique leg	+ +	+	—	—	III	B. Coli.
3" transv. shoulder	+ +	+	—	—	III	B. Coli.
3" transv. wrist	+ +	+	—	+	II	Haem.coag. + ve. staph. (sensitive)
6" oblique above knee	+	+ +	—	—	II	Non-haem. strept.
2" dorsum foot	+	+	—	—	II	B. Coli.
8" vertical shin	+	+	+	—	II	Ps.pyocyaneus.
5" oblique thigh	+	+	—	—	II	B. proteus: Gram — ve. cocci.
6" vertical thigh	+	+	—	—	II	B.Coli. Non-haem. strept.
5" transv. shoulder	+ +	+	+	—	II	B.proteus: Gram-ve cocci.
3" oblique chest	+	—	—	—	II	B.Coli: Non-haem.strept.
7" oblique thigh	+ +	+	—	—	II	B. Coli. Clostridia.
5" oblique thigh	o	—	+	—	II	Sterile.
3" transv. shin	+	+	—	—	II	Not done.
2" oblique ankle	+ +	+	—	—	II	B.Subtilis.
3" T and T calf	o	+	—	—	II	Not done.

REPORT ON THE SUTURE OF WAR WOUNDS

By Lt.-Col. R. Dudley Jones, RAMC, Officer i/c Surgical Division, 115 *(Br.) General Hospital*

The outstanding fact which has been noted at this hospital is that practically all cases arriving here have wounds which are ready for secondary suture. These cases have received parenteral penicillin and one of the sulpha drugs from the time they reached the CCS level, and on arrival here are clean and starting to granulate. It has been unfortunate from the statistical point of view that despite patients starting off from the CCS labelled "No. S", by the time they have reached here they have nearly all been given one of the sulpha drugs.

However, there is no doubt in any of our minds that since the introduction of penicillin the picture has changed considerably. Whereas previously a fairly extensive wound, which had been dealt with by the forward surgeon and a course of sulphonamide started, arrived looking healthy, it was found unwise to close this immediately; and very often one had to wait until it granulated up, when a skin graft became possible. Now a similar wound can be sutured in its very early stages with a full measure of confidence and even if, in the really difficult cases a small drain is left in one corner of the wound, or the wound edges have to be brought together under tension, a considerable amount of progress is gained as the raw area is reduced and subsequent treatment rendered much more easy, at the same time reducing the risk of secondary infection.

It is considered that the use of penicillin has very considerably reduced the time interval between the primary excision and delayed primary or secondary suture, without running the risk of a flare up of general infection or breakdown of the wound. Patients who have not received prophylactic penicillin definitely show a higher degree of sepsis and secondary suture has had to be delayed.

Variation in the rate of healing dependent on the interval between wounding and operation.

There are two distinct features to be considered here:

(*a*) The interval between wounding and primary operative treatment, *e.g.*, excision, removal of FBs, trimming, enlarging, draining, etc., plus starting penicillin treatment;

(*b*) The interval between this operation and secondary suture or delayed primary suture. It is felt that the most important factor is the interval between wounding and first toilet. Unfortunately it has not been possible here to separate these two factors and the figures which are given below are for the interval between wounding and secondary suture. It is felt, however, that the sooner the patient has his first treatment the better for the result.

Table I

RESULTS RELATED TO TIME INTERVAL BETWEEN WOUNDING AND SUTURE (239 WOUNDS)

Interval between wounding and opn.	Local Application	Total Cases	Grade I	Grade II	Grade III	Per cent Success
1 — 7 days	Penicillin	166	136	20	10	94.0
8 — 14 days	Penicillin	60	48	7	5	91.7
15 — 21 days	Penicillin	13	11	2	0	100.0

VARIATIONS IN THE RESULTS DUE TO THE CLINICAL CONDITION OF THE WOUND (CLEAN OR DIRTY)

Many wounds that appear dirty are in fact suitable for suture, while in other cases the reverse is true. A wound with a fibrinous exudate, blood clot, necrotic fascial tags, and perhaps a little sloughing of the skin edges, is still considered clean, and with a minimal amount of surgery can be safely sewn up. If, on the other hand, despite the relatively clean appearances of the wound itself, there is a considerable amount of inflammation in the surrounding tissues or a copious discharge, then it is considered wiser to leave the wound open for a few days more, in the meantime continuing with intramuscular penicillin.

Table II

EFFECT OF VARIATIONS IN SURGICAL PROCEDURES (33 WOUNDS)

Type of operation	Total Cases	Grade I	Grade II	Grade III	Per cent Success
Trimming of edges with or without under-cutting	19	16	3	-	100.0
Excision of wound or removal of M.F.B. and/or plastic flap	14	9	3	2	85.7

Despite the small number of cases actually quoted in the above table we are all convinced that the minimum amount of surgery gives the best results.

Technical difficulties. It is agreed by all the surgeons here that tension is probably the most consistent technical difficulty which leads to partial breakdown or failure. Even if this occurs a considerable amount of ground has been gained in the reduction of the size of the wound. Closing wounds over subcutaneous bones or tendons, provided there was a fairly adequate blood supply and no tension, gave rise to no particular difficulties. One small point - it was found that wounds of the axilla did very much better if the arm was kept away from the side by means of a light splint in order to overcome the moisture and heat from the axillary fold.

TABLE III

RATE OF HEALING IN VARIOUS AREAS

Site of Wound	Total cases	Grade I	Grade II	Grade III
Trunk	7	5	2	—
Arm	12	10	2	—
Leg	20	14	4	2

Unfortunately not a very large number have been selected for the above table, but from personal observation of the three surgeons the rate of healing would seem to be in the following order: face and scalp, neck, arms, trunk (excluding buttocks), upper leg and lower leg, buttocks and feet. The above figures would tend to support this.

If a FB is present and has to be removed there is a greater tendency for the wound to break down; the more the tissues have to be disturbed searching for it, the greater is this tendency. It has been found advisable in this case to remove the FB at one operation and resuture at a subsequent time.

The results are very definitely dependent on the skill of the surgeon. No amount of penicillin or any other antiseptic will make up for poor surgery.

TRANSFER OF PATIENTS—EFFECT ON SUTURED WOUNDS

Quite a large number of cases have arrived here with the sutures still in and the wounds all in good condition. This applies to the

smaller wounds, and the old teaching still holds good, that the patient must be held long enough to make sure that the wound is not going to flare up (4–5 days) and it must be kept in a state of rest during transport. Provided these conditions are satisfied there would seem no disadvantage in evacuating a patient after the fourth day. This statement is based on an evacuation of 30–150 miles and perhaps taking up to twenty-four hours.

BACTERIOLOGICAL INVESTIGATIONS

Routine swabbing of wounds during a rush-period proved impossible and they were dealt with on clinical appearances only. This proved quite satisfactory. The odd case which broke down was swabbed and the sensitivity of the pathogens to penicillin tested.

FAILURES

Any or all of the factors mentioned may cause a breakdown of the wound. The most common of these we consider is excessive tension.

There is a general dislike of using local anæsthesia for cases requiring secondary suture. All the surgeons here feel that the results are not so good as with a general anæsthetic and an attempt is being made to collect figures to prove this.

I wish to acknowledge the help of Major J. G. Bonnin and of Captain W. H. H. T. de Wytt in conducting this investigation.

DELAYED SUTURE OF WAR WOUNDS WITH AND WITHOUT THE AID OF PENICILLIN

By Lt.-Col. A. B. Kerr, RAMC, Officer i/c Surgical Division and Major F. F. Rundle, RAMC, Surgical Specialist, No. 23 (Scottish) General Hospital

This report summarises the results of delayed suture of 280 war wounds at an Advanced Base Hospital in the period January 5, to March 13, 1945. In general the wounds were very clean on arrival at this level and with few exceptions they could be closed forthwith. The exceptions, amounting to some 5 per cent of uncomplicated wounds, were those presenting acute spreading infection or deep sepsis as indicated by induration or abscess formation. The series includes all uncomplicated wounds sutured by us with the exception of one patient evacuated to the United Kingdom on account of other lesions before the result could be assessed. We have excluded from the series partial sutures, sutures carried out on amputation stumps, sutures over fractures, and two wounds in which subsequent break down was clearly due to a retained foreign body. The average maximum diameter of the wounds sutured was 6.0 cm.

One of us had experience of a large number of wounds at the same evacuation level in the Middle East. The clean appearance of the wounds here is in sharp contrast with the infection which prevailed there. We are not in possession of sufficient data regarding all the factors involved to allot the credit for this change, but there have been two obvious improvements, the use of prophylactic penicillin and the general practise of the long-preached doctrine that wounds should be inspected only when some clear indication is present.

RESULTS WITH LOCAL PENICILLIN AND "NUFLAV"

The results of treatment by penicillin and "Nuflav" (sulphathiazole and proflavine) are shown in the following table.

Agent	Total	Grade I	Grade II	Grade III	Percentage Success
Penicillin	177	141	21	15	91.5
"Nuflav"	59	49	8	2	96.6
Total	236	190	29	17	92.8

Thus over 90 per cent of wounds treated by delayed suture were completely healed within twenty-one days of operation. The

apparently more favourable results obtained with "Nuflav" probably depend on several factors; this contrast agent was introduced at an advanced stage in the series when our technique had improved and when it happened that the wounds were in general more favourable; the comparison is further biassed against penicillin by its deliberate selection in a number of unfavourable grave wounds. It must be emphasised that the patients in both groups had almost without exception received general penicillin, and that in some cases this was being continued. Under these circumstances it is clear that the local application of penicillin is not essential for securing a very high proportion of successes.

RESULTS IN PATIENTS NOT RECEIVING PENICILLIN

The figures for a group of patients (PsOW) who received no general or local penicillin, but only local sulphathiazole, are offered for comparison.

Agent	Total	Grade I	Grade II	Grade III	Per cent success
Sulphathiazole	44	27	11	6	86

It should be noted that in general their wounds were less clean than in the series receiving penicillin. Even so a high proportion of successes was achieved, though significantly less than with penicillin. The probability of the difference in distribution over the three grades being significant is greater than 95 per cent.

HEALING IN RELATION TO WOUND—SUTURE INTERVAL

Interval between wounding and suture	Local Application	Total	Grade I	Grade II	Grade III	Per cent success
1 — 7 days	Penicillin	97	83	9	5	95
	"Nuflav"	31	25	4	2	94
8 — 14 days	Penicillin	49	40	4	5	90
	"Nuflav"	21	20	1	0	100
15 — 21 days	Penicillin	22	12	5	5	77
	"Nuflav"	2	0	2	0	100
over 21 days	Penicillin	9	6	3	0	100
	"Nuflav"	5	4	1	0	100

The number of patients in the last two time-periods is unfortunately small. Some falling-off in the percentage successes in the penicillin-treated cases with increasing time interval is suggested. This tendency may well be accounted for by the cessation of general penicillin in the later periods, and by the delay in suture of relatively unfavourable dirty wounds to allow of intermediate cleansing treatment.

HEALING IN RELATION TO CLINICAL CONDITION OF WOUNDS

Agent Used	Condition of wound	Total * Cases	Grade I	Grade II	Grade III	Per cent success
Penicillin	Clean	150	124	15	11	93
	Dirty	25	15	6	4	84
"Nuflav"	Clean	56	46	8	2	96
	Dirty	3	3	0	0	100

* Detail not available in two Grade I wounds, which are therefore omitted from this table.

The anticipated result is apparent in the penicillin series, namely that clean wounds show a higher percentage of successes than do dirty wounds. The number of dirty wounds treated with "Nuflav" is so small as to render the results in that series not significant.

RATE OF HEALING IN RELATION TO COMPLETENESS OF EXCISION

Only one of us maintained precise notes of the degree of excision. His results are shown in this table.

Agent	Operative Procedure	Total	Grade I	Grade II	Grade III	Per cent success
PENICILLIN	Complete excision	11	10	1	0	100
	Partial excision	28	21	4	3	89
	No excision	2	0	1	1	50
"NUFLAV"	Complete excision	4	4	0	0	100
	Partial excision	11	6	4	1	91
	No excision	0	0	0	0	—

"Complete excision" implies the removal of the whole edge and base of the wound; "no excision" that the skin edges were merely mobilised preparatory to suture. All intermediate procedures are covered by the term "partial excision" and into this group will of necessity fall all wounds with deep tracks. The results suggest that the degree of success runs parallel with the completeness of excision.

The other of us found himself, as a result of independent experience, adopting an increasingly radical excision with progressively better results. We are satisfied that excision should always be as complete as is practicable. Thus, there can be few exceptions to the rule that complete excision down to deep fascia should be done for small gunshot wounds and for larger wounds not reaching muscle planes.

OTHER TECHNICAL POINTS

While it is desirable to avoid tension in suturing wounds we have both been impressed by the excellence of healing after suture under considerable tension provided the flaps include a generous thickness of subcutaneous tissue. When the skin is thin and adequate subcutaneous tissue not available, as behind the malleoli, in the popliteal fossa and on the dorsum of the hand, the same degree of tension cannot be applied with success. In the excision of any given wound we recognise three main methods of minimising tension; the excision should be boldly elongated by which means the tension is spread over a series of sutures rather than concentrated on those at the mid point of the wound; wide under-cutting including mobilisation of the ends of the wound; and the occasional employment of relaxation incisions.

RELATION OF HEALING TO SITE

	Total	*Failures*
Back	18	0
Arm	36	3
Forearm	23	0
Buttock	26	1
Thigh	81	4
Leg	50	8
Other sites	2	1 (hand)

We do not feel justified in drawing any conclusions from these figures but comparison with other series may enable this to be done.

FOREIGN BODIES

In only three patients was a foreign body removed at the time of secondary suture. In all, Grade 1 healing occurred. Uninterrupted healing has generally occurred where suture was carried out with a foreign body retained. An inaccessible foreign body is not a contra-indication to suture.

ARE THE RESULTS INFLUENCED BY THE SKILL OF THE SURGEON?

We feel that painstaking technique is essential if the best results are to be secured. The association of a low percentage of successes and a lack of experience in surgery has been noted.

BACTERIOLOGY

The majority of wounds have been swabbed only at operation, and necessarily the treatment has been determined by the naked-eye appearance. While the bacteriological results have been of general interest, we have no evidence that fore-knowledge of them would have led to more accurate decisions.

CAUSES OF FAILURE

Analysis of our failures shows the following factors operative:—

Residual infection	5
Unfavourable site (shin or dorsum of hand)	4
Tension	3
Adjacent wounds (tension and poor blood supply of intervening skin bridge)	2
Inadequate excision	2
No factor recognised	3

SUMMARY

In this theatre of operations and with the present management of wounds in the Forward Area, a very high proportion of uncomplicated wounds arrive at the Base clean, and can be successfully sutured forthwith.

Omission of penicillin and reliance on sulphonamides lowers the proportion of successes.

A meticulous surgical technique is necessary.

REPORT ON WOUNDS TREATED BY SURGERY AND CHEMOTHERAPEUTIC COMPOUNDS

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This reports a series of cases treated by various chemotherapeutic agents. The results are set out in a series of tables. All the cases treated are not recorded because some were not fully documented and others were evacuated before the final results could be assessed. The recorded series is small, so no dogmatic conclusions can be arrived at; it only serves as a pointer and may, with other reports, allow some definite conclusion to be reached.

The report is divided into two main parts.

(*a*) General: General remarks in answer to Questionnaire in Memorandum on Surgery No 8.

(*b*) Tables: In this section questions lending themselves to tabulation are so answered. They are sub-divided into two groups:—

(i) Results of *pre*-admission therapy.

(ii) Results of *post*-admission therapy.

A. GENERAL REMARKS

1. General. No ill effects were seen from the "No S" policy.

2. The Condition of the Wounds. Their clean and healthy condition was remarkable when compared with one's experience in the Middle East. In the BLA campaign it was the exception and not the rule for wounds to be really dirty—the only exceptions being those seen in PsOW. In attempting to explain the improvement several factors must be considered:—

(i) *Common Factors. Surgery* and *chemotherapy* can be excluded for:—

(*a*) Surgery, as in the Middle East, was done by experienced and inexperienced surgeons; and

(*b*) Chemotherapy was more intensively used in the Middle East, with infinitely dirtier wounds despite its use.

(ii) *New Factors.*

(*a*) *Penicillin* is a new factor but it is not the only one, and along with it must be considered:—

(*b*) *Diet.* The soldier in this campaign is better and more scientifically fed than he was in the Middle East, where the diet ("Bully", biscuits and salt water) was unimaginative, monotonous and ill-balanced.

(*c*) *Fluid.* Dehydration was not a feature in the BLA—it was in the Middle East.

(*d*) *Infection.*

(i) *Flies.* One has not had to wage a guerrilla war with them for access to the patients' wounds in the BLA. This alone must have reduced the incidence of infection, especially cross infection, considerably.

(ii) Skin infection and low skin resistance—as evidenced by the ever present desert sore—has been conspicuous by its absence.

(*e*) *Evacuation and its Consequences.* Probably as important as any other factor. This has been shorter *in time*; therefore more adequate surgery and better holding facilities have been available sooner. No man in the BLA has had 4–5 days in an ambulance before he received adequate surgery. Nor has he had to be held in a so-called hospital for 10–14 days, through force of circumstance, lacking good food, adequate water, a change of clothing and washing facilities; lying on a stretcher with no sheets and only blood and pus stained blankets; lacking adequate nursing staff; and periodically bathed in dust when the wind rose and it drifted through smashed walls, broken windows, and doorways or tents. Nor has he had to submit to the administrations of surgeons who had to wash repeatedly in the same water—or not wash at all.

(*f*) The lessons of the other campaigns, and especially the Middle East, have been well learnt. The organisation of the surgical services have advanced out of all recognition, and the hard won professional lessons taken to heart, and passed on.

(*g*) I have yet to see a septic joint in the BLA. But in assessing sepsis in chest wounds, compound fractures, etc, it must be remembered that cases were not held and nursed to finality in the BLA as they were in the Middle East. Despite this one can definitely say that sepsis of all kinds has been less in total incidence and individual severity.

Effects Produced by Technical Difficulties.

1. Suturing wounds under tension produces:—

(*a*) Slower healing.

(*b*) Greater tendency to break down, and

(*c*) Broad weak scars.

Methods of overcoming this:—

(*a*) Closure should be done by an experienced surgeon when possible.

(*b*) Close deep fascia (when involved) as well as skin. This helps to relieve tension on the skin.

(*c*) Excise protruding muscle before closure of deep fascia.

(*d*) Use removable mattress sutures of vertical type with deep bite and no catgut.

(*e*) If there are two parallel wounds, close one at a time if there is any tension produced by closure of both. The second wound can be closed later or skin grafted at once.

(*f*) Partial closure of wound with approximation of skin edge and skin grafting.

(*g*) Flexion of neighbouring joints.

(*h*) Reduction of swelling and oedema before attempting suture.

(*i*) Wide undercutting short of devitalisation of flaps.

(*j*) The removal of stitches by instalments over a period of days. If on removing sutures there is any tendency to "give" only every second one should be removed.

2. *Suture of wounds over Subcutaneous Bone or Tendon.* Provided tension can be avoided they do well. If this is unavoidable they should be covered by whole thicknesses of skin obtained by a relief incision or pedicle graft. The relief incision can be grafted or sutured later. This is preferable to pinch or Thiersch grafting which leaves a broad scar with a tendency to adhere to underlying bone or tendons.

3. *Crutch and Axilla.* These heal well if:—

(*a*) Tension is avoided; and

(*b*) The wound is well ventillated, *e.g.*, by abducting the arm on a frame.

4. *Sacral and Pressure Areas* (*Buttock and Back*). In these areas:

(*a*) Avoid tension.

(*b*) Secure ventilation.

(*c*) Avoid pressure—keep patient off back as much as possible.

(*d*) If on buttocks, keep bowels confined for 6–7 days to avoid possible soiling and friction of bed pan. This can be obtained by emptying the bowels by enema before operation, preceded by the use of "Nepenthe" or Tinct. Opii m. 5, t. d. s. for two days

pre-operation combined with Liquid Paraffin 1 ounce t. d. s. as this helps to secure a soft motion when another enema is given on the sixth or seventh day.

Foreign Bodies should be removed if superficial or at the bottom of a sinus, but the mere presence of a FB in the depths, provided it is quiescent and causing no reaction, does not influence the result.

Effect of Skill of Surgeon. As in all surgery the results obtained depend not only on carpentry but on knowing when, how or how much; on knowing how to avoid tension, when to skin graft, and the best type of graft; and on how to nurse the patients after operation and when to remove sutures.

Anybody can do secondary sutures but anybody cannot get good results. This is borne out by the break-down of six buttock and two back wounds with grade III results in the hands of a relatively inexperienced surgeon; he failed to appreciate the need for ventilation, undercutting and avoidance of pressure. This accounts for the relatively poor figures for local and parenteral penicillin.

Can a Powerful Antiseptic Agent Counterbalance Lack of Skill of Surgeon?

In simple wounds—YES, provided the surgeon obeys surgical principles. In other types of wounds—NO.

Wounds Sutured Pre-admission. Only three cases were seen with wounds recently sutured before admission. They did well. Provided a wound is healthy on the third day with no reaction, the evacuation time is short, the wound is protected and the limb immobilized, a short journey should do no harm. This remark does not apply to large flesh wounds or to those involving pressure areas (back or buttocks). These patients should be held till the wound is well healed—this period depending on the size and number of wounds, the severity of operation, the condition of the wound(s), and the patients' general health. In any case transfer before the tenth day is undesirable. As a general principle, big fleshy wounds should not be sutured unless they can be held till healed. Wounds superficial to the deep fascia can be sutured if the provisos in paragraph 2 (page 77) can be observed.

Routine Swabs are not necessary—clinical judgment is enough. This is another argument against the inexperienced doing wound sutures of any severity. Provided there is no reaction, no surrounding oedema and the discharge is minimal, the mere presence of dead tissue does not preclude closure as such tissue can be excised.

Causes of Failure. There was no single factor, but the following causes were noted:—

Failure to observe surgical principles:—

(*a*) Failure to secure haemostasis.

(*b*) Failure to avoid tension.

(*c*) Failure to ventilate wounds and keep them dry

(*d*) Failure to avoid pressure and dead spaces.

(*e*) Failure to secure immobilisation.

(*f*) Too early removal of all the sutures at one dressing when it was obvious that the wound was still under tension.

(*g*) Allowing the patient too much and too early liberty: rest is not always easy to enforce in an otherwise healthy man.

(*h*) Failure to remove superficial FBs underlying the wound.

(*i*) Attempting to close too large wounds at one sitting, or parallel wounds under tension.

(*j*) Failure to freshen and secure accurate approximation of skin edges, with resulting inversion and subsequent failure in healing.

(*k*) The presence of underlying infection—osteomyelitis, or devitalised tendons.

The results obtained are set out in a series of tables. The tables are divided into two main groups:—

(*a*) The relationship of *Pre*-admission Agents to:—

- (i) State of wound on admission and final result.
- (ii) Pre-admission surgery and final result.
- (iii) Pre-operation culture and final result.
- (iv) Bacteriology.
- (v) Pre-admission surgery, state of wound on admission and final result.
- (vi) Culture and state of wound on admission.
- (vii) Surgery and culture to final result.

(*b*) The relationship of *Post*-admission Agents to:—

- (i) Type of operation and final result.
- (ii) Suture or skin graft and final result.
- (iii) Time of wound, culture and operation, state of wound and final result.
- (iv) Depth of wound—state on admission—final result.
- (v) Culture pre-operation and final result.
- (vi) State of wound on admission and final result.
- (vii) Post-admission bacteriology and final result.
- (viii) Bacteriology and final percentage success.

(ix) Number healed and average time to heal.

(x) Rate of healing in upper extremity, lower extremity and trunk.

(xi) Disposal of cases.

The conclusions drawn are set out under the appropriate tables.

TABLE I

RELATIONSHIP OF PRE-ADMISSION AGENT TO STATE OF WOUND ON ADMISSION AND FINAL RESULT

Pre-admission agent	Total Cases	Condition of Wound		% Clean or Dirty	Result of Suture			% success (suture)		Remarks
					Gr. 1	Gr. 2	Gr. 3			
"Sulpha" (local) **	27	Clean	17	63	14	3	—	100	88.8	
		Dirty	10	37	4	3	3	70		
"Sulpha" (local) and parenteral penicillin	66	Clean	44	66	37	4	3	93	95.1	
		Dirty	22	34	13	5	—	100		4*
Local penicillin powder	2	Clean	1	50	1	—	—	100	100	
		Dirty	1	50	1	—	—	100		
Local sulphathiazole — 1%, proflavine, and "Sulpha".	4	Clean	2	50	2	—	—	100	100	
		Dirty	2	50	2	—	—	100		
Local and Parenteral penicillin	53	Clean	28	53	27	—	1	96	87	
		Dirty	25	47	19	—	6	76		
Local penicillin and "Sulpha" by mouth	25	Clean	16	64	13	1	2	87	76	
		Dirty	9	36	5	—	4	55		
Local and parenteral penicillin, and "Sulpha" by mouth	19	Clean	17	89	17	—	—	100	100	
		Dirty	2	11	1	—	—	100		1*
Parenteral penicillin	44	Clean	34	77	33	—	1	97	93.2	
		Dirty	10	23	6	3	1	90		
TOTALS	240	Clean	159	66	144	8	7	95	90.6	
		Dirty	81	34	51	11	14	81		5*

* — No grade recorded.

** — This term is used because it was the usual term used in the field medical cards, and is was uncertain whether sulphanilamide, sulphathiazole, etc., had been given.

RESULTS AND CONCLUSIONS

1. There was a higher percentage clean (66 per cent) than dirty (34 per cent) wounds on admission with a higher percentage final success in the clean ones (95 per cent to 81 per cent).

2. The highest percentage (89 per cent) clean on admission was with pre-admission parenteral and local penicillin and "Sulpha".

3. It should be stated that parenteral penicillin, with or without local penicillin, was used in a higher proportion of deep muscle wounds, and when studying the results this fact must be remembered. It is interesting to record that a higher percentage (25 per cent) of wounds gave positive cultures in cases who had received both parenteral and local penicillin than in those who had received

parenteral penicillin only (18 per cent) (see Table 3). There is only a difference of 4 per cent in the percentage of cases who had had primary surgery in the two groups (88 per cent to 84 per cent) (see Table 2).

4. The percentage of clean wounds after treatment with:—

(*a*) Penicillin powder locally was 50 per cent.

(*b*) With the addition of penicillin parenterally it rose to 53 per cent.

(*c*) With the addition of "sulpha" by mouth instead of penicillin parenterally, it rose to 64 per cent, and

(*d*) With the addition of penicillin parenterally and "sulpha" by mouth it rose to 89 per cent.

This surprisingly rather suggests that "sulpha" by mouth is of greater value than penicillin parenterally.

It must be noted, however, that penicillin parenterally alone gave a higher percentage clean (*i.e.*, 77 per cent) than did "sulpha" with or without penicillin parenterally, or any of the above combinations excepting parenteral or local penicillin and "sulpha" by mouth.

TABLE II

RELATIONSHIP BETWEEN PRE-ADMISSION AGENT, PRE-ADMISSION SURGERY AND FINAL RESULT

Pre-admission agent	Total Cases	Primary surgery		% + or − primary surgery	Result of Suture Gr. 1	Gr. 2	Gr. 3	% success (suture)		Remarks
"Sulpha" (local)	27	+	16	59	14	2	—	100	88.8	
		—	11	41	6	2	3	73		
"Sulpha" (local) and parenteral penicillin	66	+	57	86	43	7	3	94	95.1	4 *
		—	9	14	7	2	—	100		
Local penicillin powder	2	+	2	100	2	—	—	100	100	
		—	—	—	—	—	—	—		
Local Sulphathiazole-proflavine and "sulpha"	4	+	4	100	4	—	—	100	100	
		—	—	—	—	—	—	—		
Local and parenteral penicillin	53	+	47	88	40	1	6	88	88	
		—	6	12	3	—	1	75		2 *
Local penicillin and "sulpha" by mouth	25	+	20	80	15	1	4	80	76	
		—	5	20	3	—	2	60		
Local and parenteral penicillin and "sulpha" by mouth	19	+	19	100	18	—	—	100	100	1 *
		—	—	—	—	—	—	—		
Parenteral penicillin	44	+	37	84	33	2	2	94	93.2	
		—	7	16	6	—	1	86		
TOTALS	240	+	202	85	169	13	15	94	90.6	7 *
		—	38	15	25	4	7	80		

* — No grade recorded.

RESULTS AND CONCLUSIONS

Total cases — 240;	**90.6 per cent success**		
Pre-admission surgery 85 per cent;	Final success 94 per cent	}	90.6 per cent
No surgery 15 per cent;	Final success 80 per cent	}	

1. Those that had pre-admission surgery gave a higher proportion final success (94 per cent to 80 per cent).

2. The best results were obtained with those that had parenteral and local penicillin and "sulpha" pre-admission (100 per cent success). The figures for the other groups are too small to be significant.

3. *Effect of Parenteral Penicillin.* Its addition gave better final results. This benificial effect is evident if one studies the first two pre-admission agents in the above table (success of "sulpha" alone 88.8 per cent and of "sulpha" plus parenteral penicillin 95.1 per cent) but it is realised that the groups are not sufficiently large to avoid the possibility of considerable statistical error.

TABLE III

RELATIONSHIP OF PRE-ADMISSION AGENT TO PRE-OPERATION CULTURE AND FINAL RESULT

Pre-admission agent	Total cases	CULTURE Positive and Negative		Per cent	Result of suture			Per cent success	Remarks
					Gr.1	Gr.2	Gr.3		
"Sulpha" (local)	9	+	5	55	1	1	3	40 —66.6	
		—	4	45	3	1	—	100	
"Sulpha" local, and parenteral penicillin	52	+	23	44	10	3	9	59 —82.3	1*
		—	29	56	27	2	—	100	
Penicillin local, and penicillin parenterally	36	+	9	25	6	1	2	77 — 88	
		—	27	75	24	1	2	92	
Penicillin local, Penicillin parenteral and "sulpha" by mouth	16	+	2	13	1	—	—	100 —100	1*
		—	14	87	14	—	—	100	
Parenteral penicillin	22	+	4	18	3	—	1	75 —90.9	
		—	18	82	16	1	1	94	
TOTALS	135	+	43	32	21	5	15	63 —86.4	2*
		—	92	68	84	5	3	96	

*-No grade recorded

RESULTS AND CONCLUSIONS

1. 135 wounds were cultured; forty-three gave positive and ninety-two negative ("no growth") cultures.

2. Wounds giving "no growth" cultures have a higher percentage final Grade I and II success.

3. The use of local and parenteral penicillin with "sulpha" gave the highest percentage of negative cultures (87 per cent).

TABLE IV

PRE-ADMISSION AGENT AND BACTERIOLOGY

	Sulphan-ilamide	"Nuflav" and "sulpha"	"Sulpha" and penicillin	Local penicillin powder	Local and parenteral penicillin	Local penicillin powder and "sulpha"	Local and parenteral penicillin and "sulpha"	Parenteral penicillin	Total
Staph. aureus	4	1	5	—	3	2	2	2	19
Staph. albus	—	—	3	—	2	—	—	2	7
Proteus	—	—	2	1	5	4	—	—	12
Mic: cat.	—	—	—	—	—	1	—	—	1
Gram. Neg. Bac.	1	—	2	—	—	—	2	—	5
B. Coli	—	—	—	—	1	2	—	—	3
Pyocyaneus	—	—	1	—	—	1	—	—	2
Bac. Xerosis	—	—	—	—	—	1	—	—	1
TOTALS	5 (9)	1 (1)	13 (35)	1 (3)	11 (36)	11 (14)	4 (16)	4 (12)	50

The figures refer to the organisms cultured and not to the number of positive cultures. The figures in brackets are the total numbers of wounds cultured in each group. Staphylococcus aureus was the most common organism, with Proteus second. There were more positive cultures with "sulpha" plus penicillin than with any other agent(s). There were proportionately more positive cultures with local penicillin and "sulpha" by mouth than with any other agent.

4. The addition of penicillin parenterally increased the percentage negative cultures except in the case of parenteral plus local penicillin where parenteral penicillin alone gave a better result, *viz.*:—

"Sulpha" alone and "Sulpha" plus parenteral penicillin—45 per cent "no growth" to 56 per cent "no growth".

Local and parenteral penicillin versus parenteral penicillin—75 per cent "no growth" to 82 per cent "no growth".

5. Parenteral penicillin alone gave a higher percentage negative culture than did "sulpha" alone or with parenteral penicillin.

TABLE V

RELATIONSHIP OF PRE-ADMISSION SURGERY TO STATE OF WOUND ON ADMISSION AND FINAL RESULT

Surgery	Total Cases	Condition of wounds		Per cent	Result of suture			Per cent Success		Remarks
					Gr. 1	Gr. 2	Gr. 3			
Primary surgery performed	202	Clean	152	75	139	6	7	95	92.5	5 no grade recorded
		Dirty	50	25	31	6	8	84		
No primary surgery performed	38	Clean	7	18	7	—	—	100	80.5	2 no grade recorded
		Dirty	31	82	18	4	7	75		

RESULTS AND CONCLUSIONS

1. The cases which had had primary surgery showed a higher percentage of clean wounds on admission, and also a higher percentage final success.

2. Surgery in addition to the use of a chemotherapeutic compound gave a far higher percentage clean wounds on admission than is *obtained without surgery viz.*:—

75 per cent clean with surgery plus chemotherapy, to only 18 per cent clean without surgery.

3. It is more strikingly demonstrated when the corresponding figures in Table I are used as a contrast. In that Table the percentage clean to dirty with a chemotherapeutic compound, irrespective of surgery, is 66 per cent clean to 34 per cent dirty, whereas in this Table the figures are *with surgery* 75 per cent clean to 25 per cent dirty.

This fact holds through the whole series. These percentages and those given in Table I strongly suggest that surgery is of more relative importance in obtaining a clean wound than is the drug.

TABLE VI

RELATIONSHIP OF CULTURE TO STATE OF WOUND ON ADMISSION IN 136 CASES

Total Cases	Culture Positive or negative	Per cent	State of wound	No.	Per cent	Result of suture			Per cent Success		Remarks
						Gr. 1	Gr. 2	Gr. 3			
136	+ 44	32	Clean	15	10	9	1	5	66	66	2 no grade recorded
			Dirty	29	90	14	4	9	66		
	— 92	68	Clean	72	78	67	3	2	97	96.7	
			Dirty	20	22	16	3	1	95		

RESULTS AND CONCLUSIONS

1. 136 wounds were cultured: of these ninety-two (68 per cent) were sterile and forty-four (32 per cent) gave a growth.

2. Wounds with "no growth" cultures give better final results than those with positive cultures (96.7 per cent to 66 per cent).

3. A higher percentage of wounds with positive cultures were "dirty" on admission than in the case of those with a "no growth" culture (90 per cent to 22 per cent).

TABLE VII

RELATIONSHIP BETWEEN SURGERY AND CULTURE TO FINAL RESULT

Total Cases	Primary Surgery	Culture Negative and Positive	Per cent	Result of suture Gr. 1	Gr. 2	Gr. 3	Per cent Success		Remarks
136	+ 113	+ 30	26	17	3	8	71	91	2 no grade recorded
		— 83	74	75	6	2	97		
	— 23	+ 14	61	4	3	7	50	69	
		— 9	39	9	—	—	100		

RESULTS AND CONCLUSIONS

Wounds treated by primary surgery give better final results than those which have none, (91 to 69.6 per cent).

2. Wounds treated by primary surgery give a higher percentage of negative cultures than those which do not (74 per cent to 39 per cent).

TABLE VIII

RELATIONSHIP OF AGENTS, TYPE OF OPERATION AND FINAL RESULT

Tr. = Trimmed = Freshening of skin edges and undercutting.
Ex. = Excised = Anything other than the above.

Agent	Operation	Total Cases	Result of Suture Grade 1	Grade 2	Grade 3	Percentage success	
Local penicillin powder	Ex.	61	46	5	10	83	79
	Tr.	27	18	1	8	70	
Local and parenteral penicillin	Ex.	58	39	2	17	71	75
	Tr.	16	14	1	1	94	
Parenteral penicillin	Ex.	6	5	—	1	83	91
	Tr.	5	5	—	—	100	
Local penicillin-plasma powder *	Ex.	20	17	3	—	100	100
	Tr.	15	14	1	—	100	
Penicillin–plasma, and parenteral penicillin *	Ex.	33	30	3	—	100	100
	Tr.	11	10	1	—	100	
Local S. P. penicillin powder *	Ex.	20	18	2	—	100	96
	Tr.	7	6	—	1	86	
NIL	Ex.	7	6	—	1	86	86
	Tr.	—	—	—	—	—	
TOTALS	Ex.	196	155	14	27	86	87
	Tr.	77	64	5	8	89	

* S.P. Pen. Powder is sulphathiazole — 1 per cent proflavine powder containing 5,000 units penicillin per gm. The penicillin-plasma powder contained 5,000 units penicillin per gm.

RESULTS AND CONCLUSIONS

1. Wounds trimmed gave the better results, but it must be remembered that they were the least serious and more recent.

2. Pen. plasma powder and pen. plasma plus parenteral penicillin gave the best results (100 per cent).

3. It is interesting to note that of seven wounds excised and sutured without any chemotherapeutic agent, six gave a Grade I success.

TABLE IX

RELATIONSHIP BETWEEN AGENT USED, SUTURE OR SKIN GRAFT, AND FINAL RESULT

Agent used	Operation	Total Cases	Result of suture			Percentage success	
			Gr. 1	Gr. 2	Gr. 3		
Local penicillin powder	Suture	75	55	6	14	81	79
	S. G.	13	9	—	4	69	
Local and parenteral penicillin	Suture	74	53	3	18	75	76
	S. G.	1	1	—	—	100	
Parenteral penicillin	Suture	11	10	—	1	91	91
	S. G.	—	—	—	—	—	
Local penicillin-plasma powder *	Suture	35	31	4	—	100	100
	S. G.	—	—	—	—	—	
Pen.plasma powder * and parenteral penicillin	Suture	44	40	4	—	100	100
	S. G.	—	—	—	—	—	
Local S.P. Pen. * powder and parenteral penicillin	Suture	27	24	2	1	96	96
	S. G.	1	—	1	—	100	
NiL	Suture	7	6	—	1	86	86
	S. G.	—	—	—	—	—	
TOTALS	Suture	273	219	19	35	87	86
	S. G.	15	10	1	4	73	

*See footnote at end of previous table.

RESULTS AND CONCLUSIONS

1. Suturing gave a better final result than skin grafting (87 per cent to 73 per cent).

2. Pen. plasma and pen. plasma plus parenteral penicillin gave the best results (100 per cent).

TABLE X
RELATIONSHIP BETWEEN TIME OF WOUNDING, STATE OF WOUND, CULTURE, SUTURE AND FINAL RESULT IN 280 CASES

Interval in days	Total Cases	State of wound		Per cent	Cultures: positive or negative	Result of suture			Per cent success	
						Gr. 1	Gr. 2	Gr. 3		
1–7	192	Clean	150	78	+25	134	4	12	92	90
		Dirty	42	22	—81	33	3	6	86	
8–14	50	Clean	23	46	+18	19	1	3	87	72
		Dirty	27	54	—2	14	2	11	59	
15–21	23	Clean	15	65	+6	13	1	1	93	87
		Dirty	8	35	—1	4	2	2	75	
22 or over	15	Clean	3	20	+11	2	—	1	66	86
		Dirty	12	80	— 1	10	1	1	91	
TOTALS	280	Clean	191	68	+60	168	6	17	91	87
		Dirty	89	32	—85	61	8	20	77	

RESULTS AND CONCLUSIONS

1. Apart from the 16–21 day periods the longer the pre-admission period the higher became the ratio of dirty to clean wounds, *i.e.*, from 22 per cent dirty to 78 per cent clean to 80 per cent dirty to 20 per cent clean.
2. The final result percentage success fell from 90 per cent to 86 per cent in the 22 day period.
3. With an increasing interval before admission the proportion of positive cultures increased, viz., from 25 to 81 in 1–7 days, to 11 to 1 in 22 days and over.

TABLE XI
DEPTH OF WOUND—STATE ON ADMISSION—FINAL RESULT

Depth of wound	Total Cases	State of wound		Per cent Clean	Result of suture			Per cent success		Remarks
					Gr. 1	Gr. 2	Gr. 3			
Skin	6	Clean	3	50	2	1	–	100	100	
		Dirty	3		3	–	–	100		
Subcutaneous	49	Clean	33	67	28	3	2	94	90	1 no grade recorded
		Dirty	16		10	3	2	86		
Superficial muscle damage	69	Clean	52	75	49	–	2	96	90	1 no grade recorded
		Dirty	17		11	2	3	94		
Deep damage	111	Clean	68	61	60	2	5	92	88	1 no grade recorded
		Dirty	43		31	5	6	85		

RESULTS AND CONCLUSIONS

1. Excepting the few "skins", there was a greater proportion of dirty wounds on admission among the deep muscle wounds (39 per cent).
2. The deep muscle wounds gave the smallest percentage final success (88 per cent).

TABLE XII
RELATIONSHIP OF CULTURE PRE-OPERATION AND FINAL RESULT

Total Cases	Culture Positive or Negative		per cent	Result of suture Gr. 1	Gr. 2	Gr. 3	Percentage success	
116	+	52	44	30	4	18	65	82.7
	—	64	56	57	5	2	97	

RESULTS AND CONCLUSIONS

Wounds with a positive culture give a poorer final result than those with a negative culture—65 per cent to 97 per cent.

TABLE XIII
RELATIONSHIP BETWEEN STATE OF WOUND ON ADMISSION AND FINAL RESULT

Total Cases	State of Wound		per cent	Result of suture Gr. 1	Gr. 2	Gr. 3	Percentage success	
278	Clean	189	68	162	6	21	89	87
	Dirty	89	32	62	12	15	83	

RESULTS AND CONCLUSIONS

1. Out of 278 wounds 68 per cent were clean on admission.
2. Clean wounds gave a higher percentage final success than those dirty on admission, 89 per cent to 83 per cent.
3. Clean wounds gave a higher proportion Grade I result than those dirty on admission, 85 per cent to 69 per cent.

TABLE XIV
RELATIONSHIP BETWEEN POST-ADMISSION-BACTERIOLOGY AND FINAL RESULT

Organism.	Total Cases	Time of Culture		Result of suture Gr. 1	Gr. 2	Gr. 3	Percentage success	
Staph. Aureus	33	Pre-op	23	17	2	4	82	72
		Post-op	10	3	2	5	50	
Staph. Albus	15	Pre-op	10	5	4	1	90	85
		Post-op	5	2	1	2	60	
Proteus	29	Pre-op	23	12	1	10	56	65
		Post-op	6	5	1	—	100	
Mic. Cat.	5	Pre-op	5	3	2	—	100	100
		Post-op	—	—	—	—	—	
Gram. Neg. Bac.	5	Pre-op	5	2	1	2	60	60
		Post-op	—	—	—	—	—	
B. Coli	5	Pre-op	4	1	1	2	50	60
		Post-op	1	1	—	—	100	
Clostridia	1	Pre-op	1	—	—	1	0	0
		Post-op	—	—	—	—	—	
Pyocyaneus	2	Pre-op	2	2	—	—	100	100
		Post-op	—	—	—	—	—	
TOTALS	95	Pre-op	73	42	11	20	72	71
		Post-op	22	11	4	7	68	

TABLE XV

BACTERIOLOGY, POST-ADMISSION AGENT AND FINAL PERCENTAGE SUCCESS

Organism	Local penicillin powder	Local and parenteral penicillin	Parenteral penicillin	Penicillin* Plasma Powder	S. P. Pen. Powder and parenteral penicillin	Nil	Penicillin* Plasma Powder	"Nuflav"
	Percentage	Percentage	Percentage	Percentage	Percentage	Pctg.	Percentage	Percentage
Staph. aureus	61	67	67	100	100	0	100	50
Staph. albus	100	50	—	100	—	—	—	50
Proteus	90	40	—	100	—	—	—	—
Mic. cat.	100	—	—	—	100	—	—	—
Gram. Neg. Bac.	100	—	—	—	—	—	—	33
B. Coli	100	—	—	—	—	—	100	—
Clostridia	—	—	—	—	—	—	—	—
Pyocyaneus	100	—	—	—	—	—	100	—

* See note at end of Table VIII.

The above table gives the results obtained by individual agents against the tabulated organisms. The figures represent percentage successes.

Proteus proved the most resistant organism; only in the case of Pen. Plasma powder was a 100 per cent success obtained. Again Staph. aureus was the most common pathogen, followed closely by proteus. Pen. plasma proved the most effective agent against Staph. aureus, Staph. albus, and proteus; S. P. Pen. and Pen. plasma powders with parenteral penicillin were equally effective against Staph. aureus.

RESULTS AND CONCLUSIONS

The poorest final results were obtained in wounds containing Gram negative bacilli and B. coli. Proteus came a close second and was the second most common organism found. Staph. aureus was the most common pathogen. Staph. aureus occurred ten times post-op., and proteus six times, out of twenty-two post-operation positive cultures.

TABLE XVI

RELATIONSHIP BETWEEN POST-ADMISSION AGENT, NUMBER HEALED, AND AVERAGE TIME TO HEAL

Agent	Total cases	Healed	Average healing in days	Per cent Healed	Remarks
Parenteral penicillin	11 2*	11 2*	9	100	* Time not noted
Local penicillin powder	76	68	10	89.5	1 healed 90 per cent in 8 days 1 healed 75 per cent in 9 days 6 not healed
Local and parenteral penicillin	74	61	8	87	1 healed 40 per cent 2 healed 95 per cent in 9 days 1 healed 90 per cent in 5 days 9 not healed
S. P. Pen. **	37	32	9	86	5 not healed
Local penicillin and "Sulpha"	3	3	11	100	
Local Pen.plasma powder	35	35	9	100	
Pen. plasma powder and parenteral penicillin	44	44	7	100	
"Nuflav"	8	5	17	62.5	3 Not healed
Nil	7	7	0	100	1 healed in 22 days
TOTAL	297	268	9	90	

** See Note unter Table VIII.

RESULTS AND CONCLUSIONS

1. The above table with its percentage healed must not be confused with preceeding tables in which the final percentage success is for those healed in less than twenty-one days. The above figures are governed largely by when the surgeon examined his wounds post-op., so little significance can be attached to them as a criterion of the rate of healing.

2. The "Nuflav" cases were well over the average time in healing and had the lowest percentage healed.

3. Of seven cases which had surgery only and no post-admission chemotherapy all were healed within an average of nine days.

TABLE XVII

RATE OF HEALING IN UPPER EXTREMITY, LOWER EXTREMITY AND TRUNK

Site	Cases Healed in 1 — 7 days	Cases Healed in 8 — 14 days	Percentage Healed in 1 — 14 days	Cases Healed in 15 — 21days	Cases Healed in 22 days or over
Upper Extremity	25	50	95	4	—
Lower extremity, including buttocks	43	69	76	20	16
Trunk	16	12	85	2	3

Wounds of the lower extremity gave poorer results than those elsewhere, giving a lower percentage healed in 1-14 days, and a larger number in the subsequent periods.

DISPOSAL OF CASES

TABLE XVIII

AVERAGE TIME TO DISPOSAL IN DAYS

SUTURED		UNSUTURED
RTU.	Average 16 days	61 cases. 1335 days. Average
Convalescent Depot	Average 17 days	21.9 days to Convalescent Depots

TOTAL RESULT

RTU. (Returned to Units)	31 cases	498 days	Average days 16
Sent to Convalescent Depot.(CD)	148 cases	2492 days	Average days 17
Evacuated to United Kingdom	87 cases		
Transferred to another Hospital	31 cases		
	297 cases		

The RTU cases were all healed, whereas the CD cases were a mixture of healed and unhealed. Even allowing for this, there was a saving of five days in their disposal, whereas the RTU ones which *were healed* showed a saving of six days. This is an understatement, for they were got back to duty in sixteen days, whereas the others only got to the CD in 21.9 days. One cannot argue that the CD cases were more severe, for only the simpler ones were not sutured. Nor can one argue that the date of RTU or to a CD is largely determined by other factors, *e.g.*, transport, or Convalescent Depots not receiving on week-ends, for it is the same for both groups. There seems no doubt, therefore, that over all a great saving in man-power hours is obtained by suturing every suitable wound.

I wish to acknowledge the help of the following officers in performing this work:

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Capt. H. D. Moore

Major. G. C. K. Reid (*Bacteriologist*)
Major. H. R. Marrett (*Anaesthetist*)
Major. H. R. Crowley (*Anaesthetist*)

DELAYED SUTURE OF WOUNDS. REPORT OF 808 WOUNDS TREATED IN THE SURGICAL DIVISION, No. 6 (Br.) GENERAL HOSPITAL

By Lt.-Col. A. G. R. Lowdon, RAMC, Officer i/c Surgical Division

INTRODUCTION

The cases here reported were all treated in the period September, 1944, to March, 1945. They comprise the majority of the soft tissue wounds in patients admitted to the hospital during that time, and are unselected except in the following respects: at periods of heavy pressure of work, mostly in September and October, 1944, a number of cases of soft tissue wounds were evacuated to UK without suture; at all times a small proportion of patients were evacuated without wound suture because of complications such as nerve involvement, or associated more serious lesions from other wounds; rarely cases have been evacuated because of the gross muscle damage although neither nervous or skeletal tissues were involved; and the more trivial wounds have usually been allowed to heal without suture.

The 808 wounds treated occurred in 555 patients and were very various in size, location and degree of infection. Care was, however, taken to ensure that there was no selection of wounds for treatment by any particular method (with one exception named below), and the analysis is presented in the belief that each group includes a sufficiently representative cross section of the types of wound to make comparison permissible. Seventy (70) of the 808 wounds were not strictly speaking "soft tissue wounds" in that they were associated with fractures, but in all these cases the fracture was judged to be of a type that would not interfere materially with

the healing of the wound (in most cases fractures of the scapula or ribs). In fact three of these seventy are regarded as failures, a result that compares favourably with the average.

The one exception to the statement that the cases were not selected for any particular form of treatment is the group of nineteen wounds treated by instillation of penicillin in solution by indwelling tubes. These were all relatively large or deep wounds with potential dead space or sepsis which led the surgeon to prefer this method of treatment to any contrast method.

TIME OF SUTURE

The judgement that a wound was ready for suture was made on the grounds of clinical observation only. Purulent discharge from the wound, or other evidence of superficial sepsis has not been considered a bar to suture; nor has some oedema of the surrounding tissues, so common and so noticeable for example in the calf. There are in fact only two main features which stand as contra-indications to suture with local drugs only; there must be no invasive inflammation present, and there must be no material quantity of necrotic tissue that cannot be excised at operation.

The majority of the wounds in this series were sutured within a few days of the arrival of the patient in hospital. Often the delay was due only to the fact that it was impossible to operate on all the cases from a convoy within two days, and many of the longer delays are due also to extraneous factors.

METHODS OF SUTURE

The technique of delayed suture cannot be absolutely standardised. According to the size, age and location of a wound more or less excision is desirable or possible, and the degree of tension in suture is equally variable. In all the cases treated by local powders, the powder was insufflated after excision and haemostasis into all recesses of the wound. Of the powders used, penicillin-sulphthiazole insufflates most easily; penicillin-sulphanilamide is satisfactory but more difficult owing to the fineness of the sulphanilamide powder; penicillin-plasma mixture presents more difficulty than either because of the larger flakes of the dried plasma, but can be improved by aseptic grinding of the plasma with mortar and pestle before use.

A more detailed discussion of the technique of wound excision and of suture may be of interest.

EXCISION. In wounds up to four or five days old the excision required depends on the previous surgery in the forward areas. More or less trimming of the skin edges may be required with the main purpose of getting flat edges for good apposition in suture.

If previous excision has been performed the edges are usually flat already and only a scrape to remove adherent exudate is required. Sometimes evidently devitalised tissue must be cut away.

By the end of the first week after wounding the edges are beginning to turn in and there may be some growth of epithelium. They must then be excised—a minimal removal of tissue to get flat surfaces suitable for suture. More or less of the granulation may be removed as judged optimal to make good closure with minimal scarring, but avoiding any excision which will make dead space.

In the second and later weeks excision of the skin edges is always desirable, and all new epithelial growth must be removed. In the smaller wounds the track is now closed and a relatively flat ulcer with granulation base presents. This, in most situations, should be excised in block, leaving a wound which is closed virtually like an incision.

In all stages if there has been much skin loss, and in most of the later wounds whether or not, some undermining of the skin edges will be required to permit closure with minimal tension.

Every wound must be treated on the merits of its size, its age and its situation on the body. For example on the buttock closure is usually easy without undermining the skin, but on the forearm or front of leg where the superficial tissues are less plentiful and less mobile, closure is more difficult and undermining more often necessary.

SUTURE. In the great majority of the cases reported the suture has been made with silk worm gut. In a few cases, usually on the scalp, the hand or in flexures, linen thread has been used. One or more vertical mattress sutures are nearly always required to take tension and evert the skin edges. Buried sutures in the muscle and fascia have been reduced to an absolute minimum. Rarely some plastic procedure such as swinging a hinged flap has been used to help closure without tension.

Drainage of the closed wound has seldom been employed and then usually by surgeons who had not yet learned confidence in the procedure. In the few wounds where it is judged that drainage is desirable the indwelling penicillin tube through a separate stab wound for daily aspiration and instillation of penicillin is to be preferred.

STANDARDS OF SUCCESS

In assessing the results of suture in this series three grades were used as follows:—

Grade "A" Primary union without any clinical inflammatory reaction.

Grade "B" Complete union within fourteen days but with some transient redness of the wound edges or suture points, or early moistness of part of the suture line not amounting to separation.

Grade "C" Disruption of the suture line in any part.

Grades "A" and "B" are regarded as successful results (together corresponding to Grade I in Memorandum on Surgery No. 8). Grade "C" is classified as failure. It is to be emphasised that this grade includes several wounds which broke down in less than one quarter of their length and some which were actually healed within twenty-one days. It is regretted that the records kept do not permit valuable analysis of this "partial success." (Grade "C" corresponds, therefore, to grades II and III in Memorandum on Surgery No. 8).

RESULTS

TABLE I

RESULTS RELATED TO AGENT USED

Agent Used	Total Cases	Grade "A"	Grade "B"	Grade "C"	Percentage success
Penicillin-Sulphathiazole Powder	358	274	66	18	95
Penicillin-Sulphanilamide Powder	108	87	16	5	95
Penicillin-Sulphamethazine Powder	10	9	0	1	90
Penicillin-Plasma Powder	276	223	35	18	94
"Nuflav"	37	14	10	13	65
Penicillin by tube	19	10	8	1	95
TOTALS	808	617	135	56	93

There appears to be no significant difference in the results with penicillin and the various sulphonamide powders, penicillin-plasma powder, and penicillin solution by tube, but the results with "Nuflav" (Sulphathiazole-Proflavine Compound) are notably less successful. In view of this the "Nuflav" results are excluded from most of the subsequent analyses. In considering the 94 per cent success that was obtained with penicillin-plasma powder it should be remembered that most of the wounds treated had been dressed with sulphanilamide powder at some stage before operation. The impression received was that the sulphonamide containing powders were more reliable.

Some of the tables which follow do not include all of the 808 wounds shown above; in some cases this is due to the exclusion of the "Nuflav" results (Table IX) or penicillin tube results (Table VIII); in others to the fact that the relevant information was not

available for all cases (Tables II and IV); in most cases it is because the analyses are based on the 554 wounds treated after January 1, 1945 for which more detailed records were kept on those particular aspects (Tables III, V, VI, X and XI).

TABLE II

RESULTS RELATED TO PREVIOUS TREAMENT

In patients who had previously received	Total no. of wounds	Success	Failure	Percentage success
Penicillin 100,000 units or more and sulphonamide 10 grms or more	162	156	6	96
Penicillin 100,000 units or more and no sulphonamide	103	92	11	89
Sulphonamide 10 grms. or more and no penicillin	95	91	4	96
No penicillin and no Sulphonamide	36	31	5	86

The total number of wounds (396) included in this analysis is smaller because only those cases for whom the records were judged adequate to establish the points in question are included. It would appear, surprisingly, that the omission of oral sulphonamide is more deleterious than the omission of parenteral penicillin, but the figures cannot be considered conclusive evidence of this.

TABLE III

RESULTS RELATED TO PREOPERATIVE CLINICAL SEPSIS

Clinical Sepsis	Total	Success	Failure	Percentage success
o	227	221	6	97
+	285	264	21	93
++	42	37	5	88

An arbitrary estimate of the preoperative sepsis in three degrees, o, + and ++, was attempted. The various surgeons no doubt differed in the exact criteria for each degree, but it may be said the "o" wounds were almost dry while the "++" wounds were frankly purulent. It must be remembered that no case with invasive (+++) inflammation is included.

The results in these 554 wounds show that the percentage of success even with the most "septic" wounds was such as to justify the attempt at suture; the more so when it is to be recorded that all five of the failures in the "++" group showed only partial breakdown.

TABLE IV

RESULTS RELATED TO PREOPERATIVE BACTERIOLOGY OF WOUND

The total number of wounds from which a preoperative smear was taken for culture was 244. In all cases this smear was made at the time of operation.

"A"

Result of wound culture	Total	Success	Failure	Percentage success
Sterile	103	96	7	93
With organisms	141	126	15	89

The various combinations of organisms occurring numbered thirty-six. Those associated with failures were as follows:—

"B"

Organisms cultured	Total	Success	Failure
Staph. aureus alone	28	22	6
Coliform alone	11	10	1
Staph. aureus and coliform	8	7	1
Haemolytic strep. alone	4	3	1
Haemolytic strep. and staph. aureus	3	1	2
Haemolytic strep., staph. aureus, micrococci, and diphtheroids	1	0	1
Haemolytic strep., coliform, and clostridia	2	1	1
Staph. aureus, non haemolytic strep., coliform, and clostridia	1	0	1
Staph. aureus, non haemolytic strep., and micrococci	1	0	1

These records suggest that the common dangerous organisms are the haemolytic streptococcus and staphylococcus aureus. It will be noted that one or other, or both of them, occur in all except one of the fifteen failures noted.

Analysis of all the cultures shows the following:—

"C"

Cultures including.	Total	Success	Failure	Percentage success
Haemolytic strep.	14	9	5	64
Staph. aureus	45	34	11	75

In respect of any other single organism it is found that the results are not significantly inferior to those recorded for wounds from which no organisms were grown.

It is of interest to note that B. Proteus and Ps. Pyocyaneus were each grown from five wounds all of which healed successfully.

In assessing these bacteriological findings it should be noted that paramino-benzoic acid and penicillinase were not used in the culture media.

TABLE V

RESULTS RELATED TO SIZE OF WOUNDS IN 554 CASES.

Size of wounds	Total	Success	Failure	Percentage success
Wounds with greatest cross measurement of 2 inches or under	350	330	20	94
Wounds with greatest cross measurement of over 2 inches	204	192	12	94

The greater size of a large wound involves no extra risk of failure. Some of the wounds were as small as a half to one inch in measurement; the largest were four wounds each ten inches long, all sutured successfully.

TABLE VI

RESULTS RELATED TO LOCATION OF WOUND

Location of wound	Total	Success	Failure	Percentage success
Head and neck	31	31	—	100
Trunk	98	91	7	93
Buttock	42	39	3	93
Upper limb	76	75	1	98.5
Wrist and hand	18	17	1	94.5
Lower limb	268	251	17	93.5
Ankle and foot	21	18	3	85.5

This analysis of 554 results reflects the known ease of suture of wounds on the head and neck, and the difficulty of suture on the foot. Surprisingly the results for the wrist and hand are not significantly below average.

TABLE VII

RESULTS RELATED TO PREVIOUS SURGERY IN 808 WOUNDS

Treatment	Total	Success	Failure	Percentage success
Wounds previously treated by operation in forward area	617	577	40	93.5
Wounds not previously treated by operation	191	175	16	91.9

The statistical difference between the two groups is not great (1.6 per cent) and must be qualified by the observation that the wound which has had adequate early excision and drainage is without doubt ready for delayed suture earlier, and technically is easier to close.

TABLE VIII

RESULTS RELATED TO TIME OF SUTURE AFTER WOUNDING

"A" 476 *Cases treated with penicillin — sulphonamide powders*

INTERVAL between wounding and operation	Total	Success	Failure	Percentage success
1 — 7 days	191	180	11	94
8 — 14 days	211	203	8	96
15 — 21 days	52	48	4	92
Over 21 days	22	21	1	95

"B" 276 *Cases treated with penicillin — plasma powder*

INTERVAL between wounding and operation	Total	Success	Failure	Percentage success
1 — 7 days	207	201	6	97
8 — 14 days	59	49	10	83
15 — 21 days	4	4	—	100
Over 21 days	6	4	2	67

"C" 37 *Cases treated with "Nuflaw" powder*

INTERVAL between wounding and operation	Total	Success	Failure	Percentage success
1 — 7 days	7	6	1	86
8 — 14 days	18	11	7	61
15 — 21 days	10	6	4	60
Over 21 days	2	1	1	50

These figures do not permit any definite conclusion, but suggest that successful suture is more difficult in later wounds.

TABLE IX

771 RESULTS RELATED TO EXPERIENCE OF OPERATING SURGEON

Operations performed by	Total	Success	Failure	Percentage success
Surgeons	612	579	33	95
General duty officers and trainees	159	149	10	94

These figures cannot in my opinion be considered to have any significance since the cases treated by the general duty officers are selected by the surgeons as being those in which mistakes of judgment are less likely to occur. Given this material the less experienced operator with his more anxious care for detail should produce good results.

TABLE X

RESULTS RELATED TO DEGREE OF EXCISION

Degree of Excision of wound at operation	Total	Success	Failure	Percentage success
None	76	69	7	91
Partial	339	321	18	95
Complete	139	132	7	95

The results in these 554 cases suggest that the more conservative treatment in suture of early wounds is not always advantageous.

TABLE XI

RESULTS RELATED TO TENSION OF SUTURE

Degree of Tension of wound suture	Total	Success	Failure	Percentage success
Minimal	202	195	7	98.5
Moderate	305	284	21	93
Maximal	47	43	4	91.5

As would be expected the results in 554 wounds reflect the danger of great tension in suture.

CONCLUSION

The results given above, and impressions of other aspects of this complex problem, lead me to the view that the recent revolutionary success of delayed suture of wounds must be attributed to many factors. The routine use of penicillin and sulphonamides and adequate early surgery are probably the most important items. The results of these measures are seen not only in the case of delayed suture of the wounds, but also in the remarkable infrequence of cases of invasive or serious inflammation. The results of their absence have occasionally been seen at busy periods when convoys of prisoners of war have arrived with wounds which were, by contrast, often dangerously inflammed. Some credit must also be given, however, to the high standard of nutrition and personal hygiene of the wounded men, and to improved technique in wound dressing during evacuation as well as its less frequent practice. My experience in the Middle East leads me to believe also that there are geographical and climatic factors to be considered; that the sub-tropical areas both debilitated the general health and resistance to infection of the men and provided a bacterial flora to which they had less immunity.

The benefits to the wounded men of successful delayed suture of the wounds are self evident. The immense reduction in repeated and painful dressings in the hospital wards, the absence of men who remain in hospital for months growing new and grafted epithelium, and the relative infrequency of the smelly plaster are only some aspects of the change. The patient himself is not only healed sooner, but also regains good function more easily, particularly because the scar of the successfully sutured wound is virtually non-adherent to deeper tissues.

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Major R.E. Isaac (94 wounds)

Capt. A.M. Guthkelch (32 wounds)

Major R.F.H. Hinrichson (53wounds)

Capt. H.K. Lucas, M.B.E. (21 wounds)

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I wish to thank also Colonel S. Dolan for permission to report these cases

SUTURE OF WAR WOUNDS

By Lt.-Col. E. F. Ross, RCAMC, Officer i/c Surgical Division, 12 Canadian General Hospital

At the beginning of February, 1945, it was decided again to attempt to assess the results of delayed primary and secondary suture of wounds at this hospital. Experience in this had been gained first in England after D-Day, and this type of work had formed the bulk of the surgery done since then, except during October, 1944, when overwhelming numbers of fresh casualties from the Leopold Canal and Walcheren Island battles made it necessary to do little else but primary surgery. It was felt by the surgical staff that a great deal had been learned.

A pro-forma was completed for all wounds closed and retained till the result of suture was known. The purpose of the study was to assess the value of local and parenteral penicillin, used both as a powder insufflated at the time of the second operation (suture) and also given intramuscularly. Pro-formas on 511 wounds sutured were filled out by the following officers:—

Lt. Col. E. F. Ross	Capt. H. S. Dawson	Capt. C. B. Shier
Major F. B. Plewes	Capt. L. Lewis	Capt. A. H. Maclennan
Major H. Meltzer	Major R.H.Stevenson	Capt. N. Merkeley
Capt. W. D. Whyte	Capt. A. C. Ross	Capt. E. E. Therrien
Capt. L. R. Marwood	Major J. V. Tilley	

These do not necessarily represent work done only by the officer filling out the pro-forma, since there were changes in staff during the period and many wounds, especially those presenting problems, were operated upon by the surgical specialists. The pro-forma had been issued before the Memorandum giving 21 Army Group standards was received. Evaluation of success or failure of the closure was thus on a somewhat different basis.

Class (1) Completely healed and dry on removing sutures.

Class (2) Moist, slight exudate, but healed in two weeks.

Class (3) Partial failure; less than half of suture line broken down.

Class (4) Complete failure.

It was felt that our Class (1) and (2) categories came within Grade I as defined in the 21 Army Group Circular, that some of Class (3) and all of Class (4) came under Grade III, and the remainder of Class (3) came under Grade II. No further attempt was made to evaluate partial success or failure.

The men with the 511 sutured wounds comprising this series all remained in this hospital long enough that the success of healing of the skin could be ascertained. By our classification 371 wounds were Class (1), 106 wounds were Class (2), twenty-three were Class (3) and eleven were Class (4). Thus 477 (94 per cent) were successful (Grade I), and thirty-four (6 per cent) were unsuccessful by 21 Army Group standards. Modifying this, perhaps, to add a greater portion of failures, were a number of large severe wounds evacuated to England. These were often sutured here, but the wounds were not examined before leaving this hospital. They were in plaster casts, and usually were compound fractures of the long bones, but free of fever and pain before they were transferred; such wounds are not included in this series as the final results are not known. These severe injuries were closed before evacuation because it is firmly believed that delay beyond a week after primary surgery adds seriously to the risk of failure to obtain rapid healing of the skin, and therefore to the risks of chronic infection.

PRIMARY SURGERY

During this period under study, the preponderance of wounds sutured at this hospital had primary surgery here also. The fundamentals of this operation are generally agreed upon. The object is adequate incision of skin and fascia properly to excise muscle, and drain the depths of all ramifications of the wound. Skin is rarely excised, and then only in minimal amounts so that plastic procedures at the second operation are comparatively rare. Packing is done with plain gauze (with selvedge edge) for drainage, *not* distension, of the injured area to its depths. Plaster of Paris casts were applied if the wound involved muscle, for only by such complete immobilization was the absence of clinical inflammation at the time of closure obtained. The number of skin grafts done in the period was too small to justify separate consideration. It was found that skin edge necrosis was rare if suture was done early on these wounds.

Compared with our experience in October, 1944, when patients were admitted having been operated upon by German surgeons, the prisoners in this series were much less often infected and had wounds comparable, both on admission and on discharge to the cage, with those of Allied patients.

It seemed evident that the reasons for the grossly infected wounds and the debilitated feverish patients seen six months previously

had to do with fundamental differences in surgical practice on the part of German doctors, rather than the lack of penicillin, differences in nutrition, or soil or climate, etc. German-treated wounded had undergone excision rather than incision of their wounds, tubes were used rather than light packing, daily dressings had been done, and plaster casts applied only if bone was broken. Many had been closed at the primary operation.

RESULTS OF SUTURE

The results of wound suture are tabulated below in terms of the use of intramuscular penicillin (intravenous penicillin was not used in this series).

Use of penicillin Intramuscularly	Number of wounds	Grade I		Grades II and III		Percentage Success
		Class (1)	Class (2)	Class (3)	Class (4)	
None	92	57	26	8	1	90
Before suture only	257	194	53	5	5	96
After suture only	7	4	2	0	1	90
Before and after suture	155	116	25	10	4	90
TOTALS	511	477		34		93

In considering these results certain factors must be appreciated. Only wounds severe enough to warrant it were given penicillin before or after primary surgery. Many severe wounds did not remain in this hospital long enough for the result to be evaluated (see reasons given on page 106). But generally it can be stated that those patients who received no penicillin intramuscularly were suffering from minor wounds. Those who received penicillin only after suture also had minor wounds, the success of closure being doubtful because of inflammation present at the operation. Those who received penicillin both before and after operation were usually severely wounded, or the site, or some other factor or factors, made healing without complications less certain. Most compound fractures are in the latter group, as are extensive wounds of the buttocks and thighs. Still, the figures show that large wounds become as "suturable" as minor lacerations through the use of intramuscular penicillin.

An attempt was made to detect any difference between two bases for calcium penicillin powder. One powder was made up to contain 100,000 units of penicillin per 80 gms sulphanilamide; the other contained the same proportion of penicillin in dried human plasma. The results of suture are tabulated below:—

Treatment	Number of wounds	Grade I		Grades II and III		Percentag Success
		Class (1)	Class (2)	Class (3)	Class (4)	
No powder used	93	69	17	3	4	92
Sulphanilamide and penicillin	198	137	47	11	3	93
Plasma and penicillin	207	154	41	9	3	94
Totals	498	465		33		93

In thirteen cases the use or kind of powder was not stated. The ninety-three wounds which were not frosted with any powder include a number that were so small and clean at operation that it was considered quite unnecessary, and a few in which dusting was neglected (not likely to be serious or doubtful cases).

No significant difference in the protective attributes of the two types of powders was detected. The causes of failure showed no significant variation in the numbers due to infection. On this basis no preference for sulphanilamide or plasma as a base can be stated.

Neither powder showed evidence of toxicity or of causing local pain.

Several surgeons stated that the plasma mixture, by its stickiness, interfered with surgical technique, especially in the tying of fine ligature materials (such as "fifty" mercerized cotton) with instruments. It is considered that sometimes wound closure was annoyingly more difficult when plasma and penicillin was used. Penicillin-sulphonamide powder is generally preferred and most surgeons are using it only now.

It was noted that the sprays became clogged more frequently when they contained plasma. When first used plasma was thought to lessen bleeding. After further experience this haemostatic effect was considered absent or negligible.

The use of small rubber tubes for instillation of penicillin solution locally is becoming more and more rare at this hospital, and it was not done during this period.

CAUSES OF FAILURE

There has been much thought and discussion by the surgical officers on the subject of wound suture. It is agreed that the fundamentals are generally recognised. If the proportion of failures is to be lessened, meticulous care is not too great a price to pay. The causes of failure as revealed in this series are sometimes avoidable, and they are the features discussed.

PRIMARY SURGERY. Inadequate primary surgery often meant that the first operation had to be done over again. Unless patients were feverish or complained of pain or bleeding, their wounds were not seen by anyone after the dressings were applied in the operating room until they were removed in the operating room preparatory to suture.

The most common fault in the first operation was inadequate incision. Unless the depths of the wound are seen, foreign bodies (especially clothing) may remain and drainage of blood and exudate is inefficient and infection is encouraged. Especially is this true in operating rooms where lighting is imperfect and instruments and assistants are in short supply.

The removal of too much skin is done by surgeons who have not had the opportunity to suture war wounds and watch them heal. If the surgeon is busy it is better that no skin at all be excised. Dead skin is not a good culture medium and its presence is not a cause of toxicity, nor a reason for witholding wound closure from an otherwise well-treated wound. The tendency is to over-estimate the amount of seriously damaged skin. Therefore the overworked forward surgeon should limit his wound treatment to incising skin, excising damaged muscle and fat, incising fascia, and inserting gauze lightly and carefully so that all parts of the wound drain. Necessary skin trimming can be done just as well at the second operation.

Packing should always be done, but to avoid misconception it should be stated that it is a drainage system rather than a packing. In this unit most surgeons use plain fine-mesh gauze *lightly* placed into all corners of the wound. The object of incision at the first operation may be nullified by the placing of vaseline gauze or tulle grass over the skin, for sealed beneath such a pressing loculations of blood clot and serum form excellent culture media. That more of these wounds are not grossly infected is a tribute to the bacteriostatic power of penicillin. Most such wounds grow coliform rods or pyocyaneus on culture. One man with a large thigh wound arrived here with a staphylococcal septicaemia that did not respond to penicillin but did subside with sulphadiazine.

Immobilization in plaster casts adds much to comfort, especially while travelling, but is more important in the control of infection and minimizing mechanical causes of inflammation. It is appreciated that the application of plaster of Paris casts to all wounds is time consuming, but, using absorbant padding liberally, adequate plasters can be turned out quickly by orderlies and assistants, and with practice can be put on as rapidly as bandages or adhesive straps.

The least inflamed large wounds are often those associated with compound fractures of the femur or tibia, after transportation in a Tobruk splint. Ideally, every wound that penetrates deep fascia should be put in plaster at the primary operation.

TENSION. Skin loss may necessitate grafting rather than suture, or at least plastic procedures, in order to close the skin at the second operation. Yet with post operative support by plaster, wounds closed with a great deal of tension often heal without necrosis of skin margins if those margins have been treated gently. Longitudinal incisions of the posterior thigh spread widely by the weight of the muscles deep to them, but there is sufficient skin for successful simple suture.

TIME. After a week has elapsed from the first surgery, granulation tissue and fibrosis have progressed so that suture must be prepared for by more excision, under-cutting and freshening of skin margins. But this adds the risks of haematoma formation, necrosis and infection to the operation—all factors increasing the chance of failure.

DEATH OF SKIN. The shape of the wound may be such as to jeopardize blood supply to skin margins. T-shaped wounds are especially prone to this danger, as are flaps swung on too narrow a pedicle.

The placing of sutures at just the right depth, the right distance apart, and the right tension is difficult and time consuming. The objective is skin apposition by the least number of stitches at the least tension. One safeguard is to select the finest suture material that will do the job without breaking.

SITUATION OF WOUND. Among the failures in this series were a high proportion of wounds of the axilla, crutch and toes—all difficult places to cleanse properly and immobilize. Another anatomical situation of doubtful suture success is the chest wall over the scapula. Sulphonamide as well as penicillin for prophylaxis in lower trunk wounds is thought to lessen infection by penicillin-insensitive organisms.

SUTURE TECHNIQUE. The operation for closure is considered "an operation of election like herniorrhaphy". Therefore aseptic technique in all its aspects must be brought as close to ideal as is possible. The time factor means that most wounds must be sutured in hospitals that are "in the field" and therefore overcrowded, always short of supplies (by civilian or home military hospital standards), and hurried. Nevertheless, if the occurrence of haematomata, wound infections, and other causes of failure are to be kept to a minimum, the best possible accommodation, preparation and care must be provided.

Infection is still the commonest cause of delay in wound healing. It was a factor in twenty of the thirty-four failures in this series. Intramuscular penicillin is continued till the time of suture if it has been started, and so is sulphonamide by mouth. Wounds are not inspected in the overcrowded wards. The minimum number of people are allowed in the operating rooms and abscesses and infected cases are operated upon in a separate room.

Since only minor fractures are given definitive treatment here, no results regarding the effect of penicillin on union of bones are presented. The few civilian and allied troops with major fractures kept here show no noticeable difference in this regard between compound and simple fractures.

The remaining foreign body has shown no influence on success or failure of suture in this series. Foreign material remaining in a wound may show that the first operation was inadequate, but small fragments of metal should often be left if their removal would mean much more tissue trauma than is necessary to drain the wound properly. If the wound is clinically not inflamed it is closed at the second operation, unless the foreign body appears likely to cause trouble because of its position or size. If a foreign body is removed at the second operation the wound is closed if clinical inflammation is absent.

BACTERIOLOGY. Routine cultures of wounds are no longer done, as so many taken at the primary or suturing operation have shown pathogenic organisms on culture in the past. The bacteriology of the wound is not considered a useful aid in deciding whether closure should be completed or not, or whether a drain should be left in for twenty-four or forty-eight hours. Many routine swabs show Cl. Welchii, yet no case of gas gangrene has occurred in this hospital after suture, nor has gas gangrene of a clinically severe nature been seen if main vessels have not been ligated.

Three cases in this series failed because of pyocyaneus infection. All were successfully sutured or grafted following dressings with acetic acid for a few days. Phenoxytol did not control this infection in our experience.

TO IMPROVE RESULTS. To increase the percentage of success after suture of war wounds, it is felt that increasing meticulous care in many directions must be taken. The basic principles of the first operation—sufficient incision in the right axis, proper packing, sufficient immobilization, and frequent use of prophylactic penicillin and sulphonamides are a sine qua non. The perfection of this work will always depend on the experience and conditions under which the first surgeon to see the wounded men is working. The same factors of overcrowding, hurry, fatigue, insufficient supplies and

assistance may also influence the second operation, though to a lesser degree, as the patient is likely to have reached a base hospital by the time it is due. Thus improvement in technique and care is not always practicable, but the aim should be to approach the technique of the best civilian orthopaedic hospital in carrying out this operation.

PROPHYLACTIC PENICILLIN

Penicillin provides a means of avoiding the consequences of the imperfect conditions under which military surgery must always be done. The greater the delay in reaching the operating table, the longer the route of evacuation, the busier the surgeons, the more overcrowded the surgical units, the greater the indication for prophylactic penicillin and sulphonamides. The higher the proportion of wounded that receive penicillin, the higher the proportion of wounds that can be sutured within the optimum period, and the higher the percentage of success that will follow this operation.

DELAYED SUTURES: AND NOTES ON PENICILLIN PLASMA POWDER

By Lt.-Col. R. Rutherford, RAMC, Officer i/c Surgical Division, 110 (*Br.*) *General Hospital*

The following are the results in 142 wounds treated by delayed sutures using penicillin:—

Total Cases	Grade I	Grade II	Grade III	Percentage Success
142	118	14	10	93.0 *

FAILURES

The following conclusions have been reached with regard to the complete failures (Grade III) in this series.

1. *Delay between Wound and Suture.* Four cases (one case nine days: two cases fourteen days: one case eighteen days).
2. *Unfavourable Site.* Three cases (one over vertebra prominens: one over scapula: one on dorsum of foot).
3. *Infection.* One case—Perineum (Ruptured urethra with coli infection of urinary fistula).
4. *Extreme Tension.* One case—wound over chest.
5. *Badly Designed Flap.* One case—chest wound; lower margin of flap sloughed.

The partial failures (Grade II) were most frequent in buttock wounds and these in the scapular region, due to patients sitting on bed pans and squirming about in bed; the resaons for failure were therefore mechanical.

* Ed. Footnote. Lt. Col. Rutherford states that if the percentage success was calculated not on the basis of the number of wounds but on the number of patients the percentage success was 83 per cent. Several patients had more than one wound, and not all healed at the same rate.

GENERAL REMARKS

Foreign Bodies. If practicable, these should be removed either at the time of primary toilet or delayed suture. A foreign body in a limb in particular is prone to give rise to an abscess when the soldier is returned to duty, and the surgeon may be faced with a grossly swollen limb with induration of muscles, and consequent immobilisation of nearby joints. The man then requires rest in bed with elevation of the affected limb until all swelling subsides. The pus must be aspirated, penicillin given, and the FB accurately localised before it is approached and removed by a carefully considered route—not necessarily that of the wound of entry.

Holding Policy. Men with scalp and face wounds not sutured under tension can be evacuated in four days when the stitches are removed. Those with wounds in other regions are best held for twelve days following suture.

Condition of Wounds and Bacteriology. During the Normandy campaign the wounds appeared so fresh and clean that it was decided no infection was present in the vast majority, and that to do routine swabbings would be a useless strain on the laboratory. Decisions as to definitive treatment were always made on the "cleanness" of the wound, and this decision was amply upheld by results. Routine swabbing of wounds that appear clinically clean serves no purpose.

Minute Wounds (pepperings) with or without small retained FBs do not require excision, and if they are not oozing blood they require no dressing. A hard, dry, black eschar forms over the wound without evidence of inflammation, and epithelialisation occurs beneath the crust which drops off in due course. Occlusive dressings or vaseline gauze produce a soft scab and encourage a transudate which forms a culture medium for pathogens. On removing such dressings there is a collection of turbid fluid underneath and the wound is soggy and inflamed.

Small Wounds without Skin Loss come to us in a cleaner condition if they have been dusted with penicillin powder and dry dressed; the dressings are best retained by narrow bands of adhesive strapping. Occlusive dressings or vaseline gauze should be avoided.

Moderate Sized Wounds with Skin Loss. These do best when covered by a layer of vaseline gauze cut to the shape of the raw surface and with only a minute overlap. This in turn is covered by a slightly larger piece of sterile gauze fixed by narrow strapping applied in the axis of the limb. This method permits skin evaporation and maintains the maximum normal skin metabolism in the wounded area.

Deep Wounds, with or without Bone Involvement. Plugs should not be used, as during a battle when hurried evacuations occur the plug

may not be removed for several days. Then granulations grow into the meshes and removal is difficult, and this is still more likely to happen in open fractures if the jagged bone ends become entangled. It is suggested plugs of penicillin wax might be used by those who feel they are indicated. These would cancel themselves out in transit and supply a prolonged local application of penicillin.

Amputation Stumps. In some cases a roll of vaseline gauze had been introduced and the skin sutured lightly over this with three stitches. After two or three days granulation tissue invasion has started and the roll is quite difficult to remove without undoing the sutures. It is suggested rather:—

(*a*) That the skin be sutured lightly over the bone end *without* introducing a roll of gauze; or

(*b*) That the flaps should be rolled back (skin to skin) and the raw areas dusted with penicillin powder and covered with vaseline gauze.

Fractures of Hand Bones. In many finger injuries both tendons and joints are intact and these do not require splinting in the ordinary sense. With the advent of penicillin the outlook has changed for the better. Skin is scarce, so minimal excisions should be the rule. The wound is dusted with penicillin and covered with the smallest piece of dry gauze; this forms an "artificial scab" and no other dressing is required. The scab is dusted round the edges daily and it drops off when the epithelium has grown under the "artificial scab".

The hand and brain are so closely linked that a hand wound is almost tantamount to a brain lesion in that area subserving the injured part. In the absence of tendon or joint involvement it is of the utmost importance to show the patient he can move the injured digit from the beginning. All one wants to elicit at first is the faintest flicker, but the patient sees it, and from then on the regime is increasing active movements and no splinting. Finger fractures caused by high velocity missiles, if not sufficiently gross to "write off" the finger, cause remarkably little bone deformity. The phalanx may be shattered but there seems to be an envelope of periosteum left that, although it may be like a sieve, yet forms an efficient internal splint which is kept inviolate by the pain factor. By the time healing is complete (three weeks) a fair degree of movement has been attained, and this increases as the swelling subsides.

Grafting should only be contemplated where the skin is extensively denuded. To graft a small area, with subsequent immobilisation for two weeks, is inviting a static hand.

Metacarpal Fractures. The same remarks apply to open fractures of the middle and ring fingers. In the others the treatment is decided following assessment of the damage and deformity, with a bias towards active movements and no external splinting.

Skin Loss over Subcutaneous Surface of Tibia. Grafting is not required if the loss does not exceed four cms. across, irrespective of the length. For such cases the following method has proved successful. A skin flap as long as the skin deficiency is formed by undercutting inwards, backwards and upwards as far as is necessary. This is then sutured, if need be under great tension, and the sutures are prevented from cutting in by tying them over small pieces of corrugated rubber. The limb is encased in plaster of Paris from the tibial tuberosity to the metatarsal heads, and the patient confined to bed with the affected limb suspended above the level of the pelvis. The plaster is removed on the twelfth or thirteenth day and the sutures removed. The wound area is dusted with penicillin powder, plaster reapplied, and the patient kept in bed a further two weeks with the limb elevated. Thereafter the plaster is removed, replaced by an Elastoplast bandage applied over stockinette, the patient is allowed up, and physiotherapy instituted.

Penicillin is given as follows: 120,000 units per day for two days after operation and another 120,000 units per day for two days following removal of sutures.

One of the chief factors in the successful healing in this difficult area is elevation of the limb for the periods indicated above.

PENICILLIN PLASMA POWDER

The powder consisted of a mixture of calcium penicillin and dried plasma, ground up in a sterile mortar, to give a concentration of 5,000 units per gramme of the finished product.

The pathologist reported it was non-hygroscopic, insufflated well, and showed no "caking" propensities. It maintained its sterility well.

When used clinically it was found that the powder tended to become granular, and it was observed that the wounds tended to weep more than when penicillin-sulphonamide mixtures were employed. In view of this it was decided not to use it as a preliminary application before skin grafting. It proved a satisfactory agent for delayed sutures.

It is felt that the use of penicillin-plasma is expensive, and has no attributes to recommend it in preference to the ordinary penicillin-sulphathiazole mixtures.

A SERIES OF BURNS AND WOUNDS TREATED WITH LOCAL APPLICATION OF PENICILLIN-SULPHATHIAZOLE, "NUFLAV," AND V 187 POWDERS

By Lt.-Col. K. G. W. Saunders, RAMC, Officer i/c Surgical Division, 106 *(Br.) General Hospital*

The following series of burns was treated to see if penicillin-sulphathiazole powder produced any better results than alternative preparations used as local applications. Twenty-one burns were treated, twelve with penicillin and nine with an alternative preparation ("Nuflav" or V187 powder). The burns were all second degree with the surfaces partly covered by blisters and partly raw areas. Some had been treated in outside units first, usually with sulphanilamide cream, and the first cleansing and dressing in hospital varied from the same day to twelve days after burning. All were heat burns.

TECHNIQUE

The aim of the investigation was to treat the cases as under normal working conditions. That is after the first dressing, usually done in the theatre, subsequent dressings were done at four-day intervals in the ward with the usual aseptic dressing technique. At the original dressing, under alopon and scopolamine if necessary, intact blisters were left untouched, the whole area cleaned with saline and dried, insufflated with powder from a sterilised insufflator, and covered with sterile vaseline gauze. Swabs and cultures were taken before each treatment.

RESULTS

Judging by the figures in Table I it would appear that there is little to choose between penicillin and the alternative preparation.

TABLE I

Preparation used	Total of Cases	Time of healing (in days)				
		1—7	8—14	15—21	22—28	28 +
Penicillin	•12	1	4	3	2	2
Alternative Preparation	9	--	5	2	--	2

This did not tally, however, with clinical observation as burns treated with penicillin had a much cleaner and dryer appearance during healing than the others. Two cases had identical bilateral lesions, one on the forearm and one on the hands, and were treated on one side with penicillin and on the other with "Nuflav". The forearms showed slightly better healing on the penicillin side, the hands a marked difference. The hand treated with penicillin after nine days was dry and clean, and healing with no exudate; the one treated with "Nuflav" showed healing only in places, while most of the area was moist and covered with creamy exudate. The case in Table I treated with penicillin that healed under seven days was grossly contaminated with mud all over a fairly large raw area on the back of the hand and fingers. It was dry, clean and healing in four days and healed in seven days. Of the four cases taking over twenty-eight days, three were healing slowly at the end of that period and were evacuated to UK while the fourth was healed by the forty-third day.

BACTERIOLOGY

The predominant organism was the staphylococcus as shown in Table II, while haemolytic streptococci were found in only two cases.

TABLE II

Organisms	Number of burns in which found
Staphylococcus	
Coag. +	12
Coag. —	12
Haem. Streptococcus	2
Non-Haem. Streptococcus	—
Diphtheroids	2
B. Proteus	1
B. Subtillis	2
B. Coli	1

The most noticeable and rather surprising fact was that none of the preparations used seemed to have any marked effect on the growth of the organisms. In two burns growing haemolytic streptococci and treated with penicillin, one was controlled and the organisms disappeared, while in the other they persisted in subsequent dressings. Table III shows that out of fifteen cases in which staphylococci were present growth persisted in all but two. These were both cases treated with penicillin.

TABLE III

Effect on Growth of Staphylococci

Preparation	Total	Controlled	Not Controlled
Penicillin	7	2	5
Alternative preparation	8	—	8

This persistence of organisms did not seem to produce a marked detrimental effect on healing time as fifteen out of the twenty-one burns were healed in three weeks. But it does lead one to conclude that in the method employed the substances were not exerting their true bacteriostatic or bactericidal effect.

SENSITIVITY

Three cases developed local sulphonamide sensitivity, one with penicillin-sulphathiazole and two with "Nuflav" (a proprietary preparation of proflavine and sulphathiazole). All showed very slow healing with persistence of organisms (one streptococcus, two staphylococcus) and the dermatitis cleared quickly on changing the treatment to a penicillin spray.

SUMMARY

1. Twenty-one cases of second degree burns have been treated with local applications of penicillin-sulphathiazole powder, "Nuflav" and V187, after preliminary cleansing with saline.

2. The investigation was carried out under normal working conditions with subsequent dressings in the ward.

3. Results show that penicillin-sulphathiazole showed better results than the alternative preparations.

4. None of the preparations used adequately controlled bacterial growth, and it is felt that the method of application adopted does not utilise the full effect of the preparations.

I am grateful to Major J. C. F. Lloyd Williamson and Capt. (Miss) C. J. T. Jamieson for their help in work on these cases.

COMPARISON OF RESULTS OF DELAYED SUTURE USING PENICILLIN AND AN ALTERNATIVE PREPARATION LOCALLY

This report deals with eighteen flesh wounds unassociated with fracture treated by delayed suture after insufflation with penicillin-sulphathiazole powder in eight cases and with an alternative preparation ("Nuflav", V187, or Sulphanilamide) in ten cases. The time between wounding and suture varied from one to thirty-nine days. It is too small a series on which to be dogmatic, but certain conclusions can be drawn. Suture and subsequent dressings were done in the theatre under field (tented) conditions. Most of the cases had a course of oral sulphanilamide after suture, but none had parenteral penicillin.

RESULTS

The grades used are those suggested in the official Memorandum. In the first place it is seen from Table I that fourteen of all cases were healed in twenty-one days (78 per cent) which amply justifies the practice of secondary suture with whatever help. Discriminating, the table shows that the wounds treated with penicillin were more quickly and more completely healed than those treated with alternative preparations. Clinically it was noticeable that during healing in using penicillin there was an absence of any inflammation of the skin or suture holes, while with the alternative preparation this was invariably present. Even in the two cases shown as healed in Grade I using an alternative preparation this was so, although the inflammation had cleared and the wound was dry in fourteen days. In comparing the various substances the figures for the percentage of successes (Groups I and II) coincide with the clinical impressions received while treating the cases.

TABLE I

Preparation	Total no. of cases	Grade I	Grade II	Grade III	Success Grade I and II Percentage
Penicillin	8	6	2 (80 p.ct.) (80 p.ct.)	—	100
Nuflav	5	1	2 (70 p.ct.) (50 p.ct.)	2	60
V. 187	3	1	1 (50 p.ct.)	1	66
Sulphanilamide	2	—	1 (70 p.ct.)	1	50

TECHNIQUE

Best results were obtained by partly excising the wound when granulations had already appeared, taking a thin shaving of the skin edge. Undercutting of the skin is often necessary with a wound over 7–10 days old to get apposition without tension, which is important. With this technique haemorrhage is troublesome, and it is necessary to have it controlled before insufflating with powder as otherwise the latter is washed out before suture is completed. Sutures are passed deeply through skin and muscle.

BACTERIOLOGY

The organisms found on smear and culture are shown in Table II. Staphylococcus was the predominant organism and haemolytic streptococci were not found in any of the wounds. This may be due to the fact that all the cases except three had had sulphonamide in some form prior to admission. It is interesting to note that two of these exceptions were German prisoners taken over from a German hospital with no record of previous treatment. Both wounds looked clean clinically. The first was twenty days old and grew non-haemolytic streptococci. It was partly excised, skin edges undercut, insufflated with V187 and sutured under fair tension. A little pus oozed from the suture holes ten days later still growing non-haemolytic streptococci, but the wound was healed and clean in fourteen days (Grade I). The other, thirty-nine days old, was treated in a similar manner but with "Nuflav", grew B. Proteus and Ps. Pycocyaneus and healed mostly (70 per cent) in fourteen days (Grade II).

TABLE II

Organisms	No. of wounds in which found
Staphylococcus	
Coag. +	2
Coag. —	8
Strep. non-haemolytic	2
Strep. haemolytic	0
B. Proteus	3
B. Subtilis	1
Diphtheroids	3
Ps. Pyocyaneus	1
B. Coli	1

Control of the growth of organisms was demonstrated in eleven wounds by the presence or absence of organisms at subsequent dressings. The comparison is shown in Table III. Penicillin was shown to have a more marked effect than the alternative preparations.

TABLE III

Preparation	Number of wounds in which organisms	
	were controlled	were not controlled
Penicillin	3	1
Alternative preparation	1	6

Effect of time lapse. This is too small a series to draw any conclusions. The figures are shown in Table IV.

TABLE IV

Interval	Application	Total Cases	Grade I	Grade II	Grade III
1– 7 days	Penicillin	4	4	—	—
	Alternative Preparation	1	1	—	—
8–14 days	Penicillin	2	1	1	—
	Alternative Preparation	1	—	1	—
15–21 days	Penicillin	2	1	1	—
	Alternative Preparation	7	1	2	4
21 + days	Penicillin	—	—	—	—
	Alternative Preparation	1	—	1	—

COMPARISON

Although figures are not available it is strongly felt that the wounds in Normandy were much cleaner than those received in a forward general hospital in the latter part of the Middle East Campaign. Several factors were probably responsible, heat, sand and short water supply among them. Often a man would have been travelling for three to five days over bad desert roads since wounding, and the standard of exhaustion on arrival in hospital was much higher than that seen after travelling the relatively short distances over good roads in Normandy. Sulphanilamide therapy was maintained at about an equally high standard in both campaigns. In Normandy the men were in a better fed condition with consequent higher resistance to infection than the men who had been living

in the desert on hard rations. The prevalence of desert sores there was some indication of their reaction to infection. In this small series the absence of the streptococcus is striking if borne out by other reports.

SUMMARY

1. The results are given in a series of eighteen wounds treated by delayed primary or secondary suture from one to thirty-nine days after wounding.

2. Eight were treated with penicillin and ten with an alternative preparation ("Nuflav", V187 or Sulphanilamide) locally.

3. Most of the cases had sulphanilamide orally for five days subsequent to suture. None had intra-muscular penicillin.

4. Clinical observation and figures show that the healing was quicker and more free from infection in the cases treated with penicillin than those treated with the alternative preparations.

I should like to acknowledge help from Major J. C. F. Lloyd Williamson and Lieut. C. W. Maclay in certain of the cases.

PENICILLIN INVESTIGATION

By Lt.-Col. F. A. Simmonds, RAMC, Officer i/c Surgical Division, 113 *(Br.) General Hospital*

The most striking thing about the casualties of this campaign has been the high proportion of clean wounds received by this base hospital. There is no doubt that wounds were far less severely infected than those seen in other campaigns, such as the final African, the Sicilian and the early Italian. This observation applies to both flesh wounds and fractures, although it has not been our good fortune to treat many patients with severe bone injuries.

The terrain in Europe would seem to be more highly infective; the time lag before primary operation, and the quality of the surgery are the same as previously, or only slightly improved. The lines of evacuation are more easy in Europe, but these variables would appear to cancel out, and it seems apparent that the main factor causing the very marked decrease in wound infection is *penicillin.*

The results of prophylactic penicillin in this series are superior to the results of penicillin plus sulphonamide. If similar results are obtained in very large series of cases, the possibility exists that sulpha drugs may even have some antagonistic action to penicillin.

In the following tables:—

GRADE 0 = Perfectly clean.
GRADE + = Local pus, clean granulations beneath.
GRADE ++ = Frank local infection—no general signs.
GRADE +++ = Spreading infection with systemic disturbance.

TABLE I

A. PENICILLIN ONLY — Condition at first dressing

Total No.	Grade 0	Grade +	Grade ++	Grade +++
120	64 (53 per cent)	43 (36 per cent)	11 (9 per cent)	2 (2 per cent)

TABLE II

PENICILLIN AND SULPHONAMIDE

Total No.	Grade 0	Grade +	Grade ++	Grade +++
85	39 (46 per cent)	32 (38 per cent)	12 (15 per cent)	1 (1 per cent)

COMMENT

Grade 0 and Grade + sepsis are not easy to differentiate, and to all intents and purposes, are clean wounds.

If the figures be consolidated:—

Penicillin only 107 *clean out of* 120 (89 *per cent*)
Pen and sulpha 71 *clean out of* 85 (83 *per cent*)

The two +++ infections in the PEN only series were:—

(*a*) A man with a colostomy, low haemoglobin, and multiple flesh wounds. Faecal soiling occurred with one flank wound. He made a good recovery.

(*b*) A smashed foot with infection due chiefly to a vascular gangrene of the sole of the foot. There were multiple infected fractures of tarsus and ankle. The foot was amputated in this unit, and no form of chemotherapy could have saved it.

TABLE III·

B. RESULTS OF DELAYED PRIMARY AND SECONDARY SUTURES OF FLESH WOUNDS (including minor joint wounds)

Grade I — Healed at 14 days	127	79.5 per cent	Success 94 per cent
Grade II — Healed at 21 days	23	14.5 per cent	
Grade III — Not healed at 21 days (failure)	10	6 per cent	6 per cent

160 wounds are reviewed, with ten failures. Table III demonstrates nearly 80 per cent complete success and 14 per cent delayed success.

The work has been done by four surgeons; a few wounds, capable of easy closure, have been dealt with by the GDOs. No attempts have been made to evaluate the results of individual surgeons, because the total numbers were too small, and the policy to follow had been agreed.

It is unreasonable to expect primary union of skin, unless the skin edges are freshly cut; as a general rule, therefore, all wounds were excised. Where a wound was dirty or had been inadequately excised in the forward area, a complete secondary exploration and excision was performed preparatory to secondary suture; often pieces of cloth or metal were found.

Penicillin-sulphathiazole powder was used as the routine local application. Some patients had forty-eight hours to four days intramuscular penicillin as well. A few wounds were frosted with sulphanilamide only. (See Table V).

The decision to close a wound was made on purely clinical grounds. The theatres always had secondary suture or skin grafting trolleys ready, and as plasters or dressings were removed, so the wounds were assessed and dealt with.

Unless special pathology teams are attached it is impossible for the laboratory to cope with routine wound swabs, and anyway it seemed apparent that, from the practical point of view, they were a waste of time. The laboratory should help in assessing the causes of failure, and in determining the bacteriology of wounds with virulent infection.

TABLE III (a)

No. of wounds NOT excised	Grade I	Grade II	Grade III
13	9	4	0

Only thirteen wounds were closed without excision; they were all small and easy, but 30 per cent had delayed healing (Grade II). The figures are too small to be more than suggestive, but all the thirteen cases came in the 1–14 day period, and the comparable figures (Table IV—with the unexcised wounds subtracted) is 12 per cent delayed healing.

TABLE IV

RESULTS ACCORDING TO THE TIME LAG BETWEEN WOUNDING AND SECONDARY SUTURE

Time Lag (days)	Number	Grade I	Grade II	Grade III	Percentage Success
1–7	77	69 (89.6 p. ct.)	7 (9 per cent)	1 (1.4 p. ct.)	98.6
8–14	60	44 (73.4 p. ct.)	12 (20per cent)	4 (6.6 p. ct.)	93.4
15–21	19	12 (63.4 p. ct.)	3 (16per cent)	4 (21per cent)	79
Over 21	4	2 (50per cent)	1 (25per cent)	1 (25per cent)	75

EFFECT OF TIME LAG

There seems a clear indication that the sooner the wound closure can be done the better the result, not only in healing but also in rate of healing. As the time lag increases, fibrosis becomes more marked, the skin is made less elastic, the blood supply of the skin edges is reduced, and a wider excision of skin becomes necessary.

All these factors increase *tension*, which in our experience seemed the chief factor responsible for the failures.

The period between the fourth day, when post traumatic oedema is subsiding, and the eighth day, is put forward as the ideal time for delayed wound suture.

TABLE V

RESULTS ACCORDING TO CHEMOTHERAPY USED

Agent used.	Sec. Suture TOTAL	GRADE I	GRADE II	GRADE III	Percentage Success
Pen.-Sulpha powder and I.M. Pen.	49	44 (90per cent)	3 (6 per cent)	2 (4 per cent)	96.0
Pen.-Sulpha powder	95	76 (80per cent)	13 (14per cent)	6 (6 per cent)	94.0
Sulpha powder	16	7 (44per cent)	7 (44per cent)	2 (12per cent)	88.0

Table V-gives results which are just what one would have predicted and it is probable that larger series of figures will correspond.

On some occasions, I. M. penicillin was given in addition to the local powder, because patients had larger and more infected wounds. In spite of this the results are appreciably better.

It is suggested that after a secondary wound excision, an inflammatory reaction occurs, with oedema, thereby increasing *tension* over the following two to three days. It is during this short period that I. M. penicillin is most useful in flesh wounds, as unless the other measures (excision and frosting) have sterilized the wound completely the increase of *tension* may mean delayed healing or failure.

On four occasions, secondary suture after frosting with penicillin powder has caused an acute "flare up" of infection locally. The removal of two sutures and a four day course of I. M. penicillin produced healed and dry wounds in fourteen days.

My impression from previous campaigns is that local irrigation through fine tubes is apt to leave small but distressing sinuses exuding gram-negative pus; it is difficult to imagine that local irrigation can penetrate to all parts of a wound.

Should Small Circular T and T Wounds Require Suture?

The following case is typical of many:—

Lt A. (1) T and T wound Rt. Flank, (2) T and T wound (superficial) Rt. Calf.

7th day: (1) Wounds in flank 2 inches by 1 inch dirty—infection +. Delayed suture performed after excision.

(2) Wounds in calf ½ inch by ½ inch—appear clean. No surgery.

17th day: (1) Both sutured wounds healed and dry.

(2) Both wounds indolent with slight infection.

27th day: (1) Healed; mobile scars.

(2) Still require dry dressing.

It seems that the quickest way to obtain healing of small wounds is by excision and delayed suture. The resultant scars stand up to trauma much better.

FAILURES

Failures seem more often due to excessive tension than to infection. Often (eight out of ten) these so-called failures succeeded in converting large wounds into raw areas the size of a penny or less. Such cases might be classified as 70 per cent or 80 per cent successes.

Four of the failures were infected buttock wounds sewn up under moderate tension; the wound swabs afterwards showed Proteus or B. Coli.

One wound became secondarily infected from a colostomy.

Two wounds were on the sole of the foot and would probably have been better skin grafted owing to the lack of skin mobility.

One large thigh wound was sutured elsewhere, evacuated after four days, and broke down completely. After cleaning up a further secondary suture was done and failed, owing to considerable fibrosis and tension; again, a skin graft would have been better treatment.

It is our belief, not borne out by sufficient numbers of figures, that cases after secondary suture require a minimum of seven and preferably ten days rest without further evacuation.

SUMMARY AND CONCLUSIONS

1. A very high proportion of wounds seen at first dressing in a BLA base hospital are clean.

2. The chief factor responsible for this striking improvement over the results seen in previous campaigns appears to be penicillin.

3. All wounds, large or small, should be closed as soon as possible, either by skin grafting, delayed suture or secondary suture.

4. The optimum time of closure appears to be between the fourth and eighth day after wounding.

5. Wounds should be secondarily excised before suture.

6. Where there is little or no tension, local frosting with penicillin powder is sufficient.

7. Where tension exists, or there is a considerable degree of infection present, a three or four day course of I. M. penicillin should be given in addition (100,000 Units in twenty-four hours).

8. Tension is the main cause of failure.

REPORT ON THE SUTURE OF WOUNDS

By Lt.-Col. D. H. Young, RAMC, Officer i/c Surgical Division, 108 (*Br.*) *General Hospital*

The first experiements with secondary suture in this hospital took place in Bayeux in August and September 1944, when local treatment by 1. Penicillin (5,000 units in 1 gm. of sulphathiazole), and 2. V187 were contrasted.

Table I gives the results of this investigation—a slightly better result with penicillin powder.

TABLE I

Agent Used	Total cases	Grade I	Grade II	Grade III	Percentage success
Pen. and Sulphathiazole	24	18	2	4	83.5
V 187	20	14	1	5	75

Table II gives the comparison of cases excised and not excised. The numbers are too small to make any generalizations, but the feeling was present that the carefully excised cases did better.

TABLE II
RESULTS OF EXCISION AND NON-EXCISION IN 44 WOUNDS

Agent Used	Method	Total cases	Grade I	Grade II	Grade III	Percentage success
Pen. and Sulphathiazole	Excised	20	17	—	3	85
	Not-Excised	4	3	1	–	100
V. 187	Excised	14	11	1	2	79
	Not-Excised	6	3	–	3	50

In Brussels original research was made on the effect of using parenteral penicillin alone. At the same time cases were treated by local penicillin — and the more severe cases by local penicillin plus intramuscular drip.

In the course of this series one penicillin drip abscess occurred, pus from which grew a pure culture of B. coli. One case of severe cellulitis of the thigh was seen following the use of repeated intramuscular injections in a forward hospital. Both cases subsided without further complications.

The results obtained from October, 1944, to March, 1945, are shown in Table III. Practically all of these wounds had at least minimal skin excision.

TABLE III

RESULTS RELATED TO AGENT USED IN 423 WOUNDS

Agent used	Total cases	Grade I	Grade II	Grade III	Percentage success
Local Pen.-Sulphathiazole	106	88	16	2	98
Local Pen. and I. M. penicillin Drip	190	162	18	10	95
I. M. penicillin drip only	88	76	11	1	99
Local sulphon.	10	7	2	1	90
Local Marfanil	6	5	—	1	83.5
Nil	23	13	1	9	61

CONDITION OF WOUNDS

Until the Battle of the Rhine crossing the only dirty wounds seen in this hospital were those in prisoners who had received neither penicillin nor sulphonamide therapy.

No significant differences were seen between penicillin or sulphonamide treated cases—but the feeling is that dirty wounds clean up more quickly with penicillin.

In the last ten days we have received numerous dirty cases coming straight through (in twenty-four to forty-eight hours) with early dressings which have had neither penicillin nor sulphonamide, or only occasional and irregular doses of either—and no surgical interference. The lack of simple surgical incision and chemotherapy has changed the picture from our normal two to four day old clean wound to the septic dirty wound.

Evidence accumulated in our research on parenteral penicillin showed that there was no significant difference in the final result whether there had been early penicillin treatment or not. But in the experiment all cases had penicillin for forty-eight hours before as well as after suturing—with a success rate of 99 per cent. In the series of local penicillin plus intramuscular penicillin drip (all of which was given after the suturing) the success rate was 95 per cent. No comparative figures about the rate of healing or recovery of function can be given.

Whether variations in the rate of healing do occur with the increasing interval between wounding and operation is difficult to assess from our results. While Table IV does not show any

variation in the cases treated with local penicillin powder, there is a definite downward tendency in the cases treated by local penicillin plus penicillin drip—and also in the untreated cases.

TABLE IV

RESULTS RELATED TO TIME INTERVALS BETWEEN WOUNDING AND SUTURE

Time after wounding	Therapy	Total Cases	Grade I	Grade II	Grade III	Percentage Success
1 — 7 days	Locan pen. S.	64	55	7	2	97
	Local + I. M. drip	114	101	8	5	97
	Nil	5	4	1	—	100
8 — 14 days	Local pen. S.	34	27	7	—	100
	Local + I. M. drip	66	56	7	3	97
	Nil	13	8	—	5	16.5
15 — 21 days	Local pen. S.	5	5	—	—	100
	Local + I. M. drip	6	3	2	1	83
	Nil	4	1	—	3	25
Over 21 days	Local pen. S.	3	1	2	—	100
	Local + I. M. drip	4	2	1	1	75
	Nil	1	—	—	1	0

Table V which shows the variations in the series doner with intramuscular penicillin drip alone is very marked if the criterion of Grade I is used. Here the time intervals taken are beforeand after ten days—an empirical number selected because one writer claimed that the best healing time was from the 5th to 9th day.

TABLE V

Time after wounding	Total Cases	Grade I	Grade II	Grade III	Percentage Success
1–9 days	42	39 (93 per cent)	2	1	98
10 days or over	40	31 (77.5 per cent)	9	–	100

These same cases broken down into the form used in Table IV show a different result.

TABLE VI

Time after wounding	Therapy	Total Cases	Grade I	Grade II	Grade III	Percentage Success
1–7 days	I.M.Pen. drip.	16	16 (100 per cent)	—	—	100
8–14 days	I.M.Pen. drip	58	46 (80 per cent)	11	1	98
15–21 days	I.M.Pen. drip	8	8 (100 per cent)	—	—	100

Taking Grade I as our criterion we have a very poor result in the 8–14 day period with a recovery in the 15–21 day period.

Logically, I can see no reason why the time interval should affect the result as long as the wound is excised and fresh tissue is utilised in the repair. The repair does require good surgery—a slap-dash method will not give as good results.

Whether a wound is clean or dirty (unless there is actual gangrenous matter which it would be unwise to excise due to its location) does not matter. As long as intramuscular penicillin is used preoperatively as well as postoperatively the results are good. We have now had several cases of abscesses and bursitis incised, emptied of pus, treated with intramuscular penicillin, and sutured successfully three or four days later.

Several cases of removal of F.B. at the time of operation have been seen, and in no case had any bearing on the result.

Evacuation of Sutured Wounds. In the last two months I have seen three sutured wounds that had not been immobilized and were moved on the fourth or fifth day. Two broke down completely and the third was very indurated and had numerous stitch abscesses; successful tertiary suture was done on the two which broke down. In one case local penicillin and an intramuscular penicillin drip was used. In the other local penicillin injections at fifteen minute intervals; these courses were given during the operation, and forty-eight hours later when the drain was taken out.

In my opinion a man should be held for seven days before he is moved following wound suture as by that time in many cases it is possible to know whether the wound has healed or not.

LABORATORY FINDINGS

With the co-operation of Major Winston Evans, Pathologist, sixty-seven wounds were studied in our recent experiment. Wounds containing coliforms and certain strains of insensitive staphylococci tended to have delayed healing and partial failure. Routine wound swabbing, while it might help in prognosis, is of little value; attention would be better focussed on the bacteriology of the failures.

In the numbers of cases given those from Bayeux were initiated by Lt-Col. Ian Fraser, D.S.O., Major B. L. Harbison and myself to start our first experiments in secondary suture.

For the large amount of work done in Brussels I must thank Major D. M. Jones, Major G. S. Ferraby, Capt. Hugh C. McLaren—surgeons; Capt. H. K. Bourns—orthopaedic surgeon; and trainee surgeons, Capt. W. F. White, Capt. A. G. Potts, Capt. J. L. Anderson and Capt. R. B. Welbourn. All had a hand in the secondary suture successes.

DELAYED SUTURE OF SOFT TISSUE WOUNDS USING PARENTERAL PENICILLIN

By Lt.-Col. Donald H. Young, RAMC, Officer i/c Surgical Division, Major R. Winston Evans, RAMC, Pathologist, and Major K. E. A. Hughes, RAMC, Pathologist i/c Penicillin Laboratory

This paper describes the results obtained by delayed primary or secondary suture in a series of eighty-two wounds occurring in fifty-five patients. The only adjuvant to the surgical treatment employed was parenteral penicillin given by continuous intramuscular drip (100,000 Oxford units in 540 cc. of sterile normal saline daily for 4–5 days), no local applications being used after admission to hospital.

The wounds involved the soft tissues and were uncomplicated by bony or visceral injuries. They were not specially selected but were consecutive cases of the type described. They varied in degree from slight to moderately severe. The presence of pus or sloughs was not regarded as a contra-indication to suture.

Systemic administration of penicillin is not economical, but the experiment was in part carried out because statements have been made from time to time that better results are obtainable by using penicillin locally rather than parenterally in the treatment of wounds; and because the method of injecting penicillin solutions through tubes is not altogether surgically sound, since the fluid may separate the surfaces one wishes to unite, and the manipulations involved increase the risk of infection with insensitive pathogens.

We have now had considerable experience in the use of both local and systemic penicillin as an aid to surgery in the suture of war wounds, and contrary to previous statements find that the latter gives as good results as the former. Table I shows the results obtained in a series of 110 wounds using local penicillin powder at a strength of 5,000 units per gram of sulphathiazole.

TABLE I

Interval between wounding and operation	Total cases	Grade I	Grade II	Grade III	Percentage success
1– 7 days	55	46	7	2	96.4
8–14 days	43	33	8	2	95.3
15–21 days	12	8	3	1	91.7

In assessing results the following standards were employed:—

GRADE I Success: wound completely healed and dry at fourteen days.

GRADE II Partial success: wound not quite healed at fourteen days but completely healed and dry at twenty-one days.

GRADE III Failure: wound not completely healed at twenty-one days.

In calculating the percentage of successes, Grades I and II are taken together.

The experiment described in this paper was planned to ascertain

(*a*) The results of employing a definite surgical technique, aided by parenteral penicillin only.

(*b*) The types and sensitivities of any infecting organisms.

(*c*) The relative concentration of penicillin in the blood and in the wound exudate.

(*d*) The effect of low concentrations of penicillin on strains of staphylococci.

(*e*) Any common factor or factors occurring in the failures, such as insensitive pathogens, etc.

METHODS AND RESULTS

All wounds were examined soon after admission and they were then cleansed gently but carefully with sterile normal saline. Administration of penicillin by continuous intra-muscular drip was instituted twenty-four hours later, and was continued for forty-eight hours before operation and for forty-eight to seventy-two hours afterwards. At operation the wound edges were freshened by removal of minimal amounts of skin; any devitalised tissue, foreign material or excessive granulations being removed. If necessary the skin edges were undercut sufficiently to facilitate approximation without undue tension, and haemostasis was secured. A small rubber drain was inserted to avoid the possibility of haematoma formation or the collection of exudate in pockets. Alternate mattress and ordinary sutures were used for closure, buried sutures being avoided. Immobilisation by light splintage or a thoraco-brachial bandage was carried out when possible. The drain was removed forty-eight hours after operation and the stitches taken out on the tenth day, remedial exercises and physiotherapy being commenced as and when considered advisable.

A small control series of eighteen wounds which were closed without local or parenteral penicillin or other adjuvant treatment is included for comparison, but it is realised that the number is too small to be of statistical significance.

The results obtained in both series are tabulated (Table II).

TABLE II

Interval between operation and wounding	Adjuvant treatment	Total Number	Grade I	Grade II	Grade III	Percentage success
5 —9 days	Parenteral penicillin	42	39	2	1	97.6
10 days upwards	Parenteral penicillin	40	32	8	nil	100
1—7 days	None	4	3	1	nil	100
8 days upwards	None	14	6	nil	8	43

Patients reach base hospitals at varying times after wounding and therefore the cases have been divided into groups according to the interval between wounding and operation. In the first group the interval varied between five and nine days while in the second ten days or more had elapsed before suturing was performed. The majority of the controls were in the latter group, and it is of importance to state that they were of a less severe character than those treated with penicillin.

In calculating the percentage success Grades I and II are both included, but it will be noted that if Grade I were adopted as the criterion, Group I (five to nine days) shows a higher degree of success *viz.*, 92.9 per cent as compared with 80 per cent in Group II (ten days and upwards). In this series it appears that the interval between wounding and operation exercised a definite influence on the resuts assessed at fourteen days, although at 21 days there was no significant difference.

In the locally treated cases this variation is also apparent, being 83.6 per cent in the 1–7 group, 76.7 per cent in the 8–14 group, and 66.6 per cent in the 15–21 group.

Dogmatic assertions cannot be based on eighty-two wounds, but nevertheless the findings are of interest. The one complete failure in the parenteral penicillin series group was a circular wound of the back 2 inches in diameter. Owing to its nature the tension produced by suture was greater than desirable, yet at ten days when the sutures were removed it appeared to be firmly healed. On the fourteenth day during remedial exercises it gaped at the point where the drain had been situated leaving a raw area $\frac{3}{8}$ inch in diameter; this was still granulating on the twenty-sixth day when the patient was evacuated.

BACTERIOLOGY

Sixty-seven of the soft tissue wounds occurring in fifty-one patients in this series were investigated bacteriologically. The wounds were first cleaned with sterile saline, and twenty-four hours later a swab was taken and cultures made on blood agar. Cultures were repeated after twenty-four hours of penicillin therapy and again when the drain was removed. Further cultures were made if a wound showed any tendency to breakdown. The distribution of the organisms found is shown in Table III.

TABLE III

Organisms	No. of times isolated at first examination	Subsequently	Total
Staphylococci Coag. +	32	7	39
Staphylococci Coag. —	4	5	9
Diphtheroids	11	12	23
"Coliforms"	17	11	28
"Micrococci"	17	4	21
Strep. Anhaemolyticus	1	0	1
Enterococci	2	0	2
Proteus	3	0	3
Pyocyaneus	0	1	0
B. subtilis	2	0	2
B. anthracoides	0	1	1

As is usual staphylococcus pyogenes was the predominating pathogen. It occurred just as frequently in the wounds of patients who before admission to hospital had received penicillin either by intermittent intramuscular injection or locally as in those to whom penicillin had not been exhibited in any form.

The characteristics of the "micrococci" were as follows. They did not retain the Gram stain. They were large cocci occurring in clusters and formed large mucoid colonies on all media tried, were coagulase-negative, formed acid but no gas in glucose, and failed to ferment lactose, mannite, saccharose or dulcitol after two weeks' incubation. They were penicillin resistant, and in two strains tested penicillinase production was found to occur. Although they appeared eighteen times among the sixty-seven wounds and were lethal to mice they did not have any significant effect on the rate of healing or the result.

PENICILLIN SENSITIVITY OF ORGANISMS ISOLATED

Penicillin sensitivity tests were carried out by a tube method using tenfold difference in concentrations between tubes. Only the results with staphylococci are included here.

Thirty-two strains of the organism were isolated at the first examination. Of these, twenty-four were normally sensitive, six were relatively insensitive, and two were not examined as they could not be separated from the other organisms present. After four days penicillin therapy nine of the sensitive strains showed an increased resistance to penicillin. This increase was at least tenfold. In view of the work of Spink and others (1) on the decrease of pathogenicity with the increase of resistance in penicillin treated organisms, it is interesting to note that none of these nine strains

occurred among the partial successes. The one complete failure showed no increase in resistance of its infecting staphylococci.

In contradistinction, two of the three strains of relatively insensitive, coagulase-positive staphylococci isolated on first examination showed a percentage of healing at fourteen days of 90 per cent and 60 per cent respectively. The third case was completely healed at fourteen days although it showed signs of breakdown at seven days. These three organisms make up 50 per cent of the total number (six) of relatively insensitive staphylococci isolated at first examination among the whole thirty-two.

Table IV shows the distribution of organisms in ten penicillin treated wounds and two controls in which only partial success occurred, while Table V shows similar findings in a further six wounds which, although they were completely healed on the fourteenth day, showed signs of breakdown on the seventh day.

TABLE IV

Case No.	Organisms at first examination	Coagulase	Sensitivity	Per cent healing at 14 days	Remarks
9	Micrococci	—	—	90	
	Diphtheroids	—	—		
13	Staphylococci	+	+	80	Mechanical factor responsible
21	Staphylococci	+	—	90	
	Diphtheroids		—		
39a	Staphylococci	+	+	90	
	Coliforms		—		
39b	Staphylococci	+	—	60	
39c	Staphylococci	+	+	80	
40	Staphylococci	?	?	90	Organisms not separable
	Coliforms				
41a	Staphylococci	+	+	90	90 per cent at 21 days. Complete failure
	Coliforms				
49b	Staphylococci	+	+	90	
	Coliforms				
54b	Staphylococci	+	+	90	
	Coliforms				
			Control Cases		
27	Staphylococci	+	+	0	Only wound
	Diphtheroids		?		
	Coliforms		—		
28	Staphylococci	+	+	0	1 of 3 wounds. Other 2 healed 100 per cent although their flora were similar.
	Diphtheroids		?		
	Coliforms		—		

+ = sensitive
— = insensitive

The letters a, b and c, where used, indicate different wounds in the same patient.

TABLE V

All cases 100 per cent healed on 14th day.

Case No.	Organisms at first examination	Coagulase	Sensitivity	Per cent healing at 7 days	Remarks
1	Staphylococci	—	+	80	On 4th day Staphs C+S—
4	Staphylococci Micrococci	+	— —	90	
35	Coliform		—	90	
51	Staphylococci Coliform	?	?	90	Organisms not separable.
54a	Staphylococci	+	+	90	On 2nd day Staphs C + S —. This was a buttock wound over a large area
55	Diphtheroids Coliform		+ —	90	

Combining Tables IV and V, partial failures at fourteen days, and relatively delayed healing at seven days, it will be seen that eight out of eighteen cases showed the combination of staphylococci and coliform bacilli. This combination was present only fourteen times altogether throughout the whole series.

Coliforms occurred either alone or in combination with staphylococci or other organisms twenty-four times and showed delayed healing or only partial success in forty-two per cent. Other combinations of potential pathogens occurred too infrequently in the series to be significant.

RELATIVE CONCENTRATIONS OF PENICILLIN IN SERUM AND WOUND EXUDATES

Comparison of the concentrations of penicillin in the blood stream and wound exudate were made in thirty-five cases. The method used was that described by Garrod and Heatley (2). The concentrations were found to be the same in fifteen (43 per cent) of the cases. In thirteen (37 per cent) the amount present in the blood was greater than in the exudate, while in seven (20 per cent) the higher concentration occurred in the wound exudate.

When the wound exudate showed a higher concentration than the blood, the difference was only slight, but when the blood showed a higher concentration than the wound, then the difference was generally much greater.

Among these thirty-five cases, with one exception, the partial failures all occurred when the amount of penicillin in both blood and wound exudate was less than 0.2 units per cc. The exception showed 0.8 units per cc. in the exudate with no demonstrable penicillin in the blood. This is thought to be due to an error in technique.

SUMMARY AND CONCLUSIONS

As described in the beginning of this paper the authors set themselves the task of answering five questions.

1. The results of employing a definite surgical technique aided only by parenteral penicillin are satisfactory, particularly in wounds which are sutured relatively early. In all, 86.5 per cent of the wounds were completely healed after fourteen days and 98.8 per cent after twenty-one days. These results compare favourably with those achieved by us when using local penicillin.

The presence of a small drain is considered to be of importance in the early stages of healing.

2. As has been found in many other series of cases, the predominating organism is the staphylococcus pyogenes. Streptococcus haemolyticus was conspicuous by its absence. The only other potential pathogen to be found in any numbers was the coliform bacillus.

3. The concentrations of penicillin in the blood serum and wound exudate showed a certain degree of uniformity, but differences do occur for reasons not yet ascertained. As long as a certain penicillin level is attained in one or other situation, the relative concentration appears to have little bearing on the result.

4. A number of relatively resistant strains were found after four days penicillin therapy. Owing to the difficulty of typing staphylococci satisfactorily it is not known whether these resistant organisms were the same strains as those found originally in the same wound. This question is being studied further.

5. In this series better results were obtained in the group of cases where suture was possible within ten days of wounding. The varying time intervals were determined by the time occupied in transit and not by holding the patients for differing periods in hospital before operation.

The presence originally of insensitive staphylococci militates against early healing, but the appearance during treatment of these organisms has little effect. The presence of coliform bacilli alone or in combination with other organisms definitely delays complete healing. The presence of this so-called "gram-negative pus" is of greater importance than has sometimes been thought.

The concentration of penicillin circulating must be kept above a certain level to achieve the desired result.

REFERENCES

(1) SPINK, W. W., FERRIS. V. AND VIVINO, J. J., Proc. Soc. Exper. Biol. and Med. (1944), 55, 210.

(2) GARROD AND HEATLEY, Brit. Jour. Surg. (1944), 32, 123.

THE RESULTS OF WOUND CLOSURE USING PENICILLIN AND CONTRAST AGENTS

By Brigadier A. E. Porritt, Consulting Surgeon, 21 *Army Group, and Lt.-Col. G. A. G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy,* 21 *Army Group*

This article is based partly on the evidence submitted in the previous reports and partly on the results of our own observations and experience. Apart from minor sub-editing the reports are presented exactly as received, and all dealing with at least fifty cases have been printed; owing to circumstances beyond their control a number of Divisional Officers could only provide information about smaller groups. In the consolidated tables, however, all figures in our possession have been included*. We have attempted to weigh the evidence carefully, but as some may not agree with our judgments and as they do not always coincide with opinions expressed in individual reports, it is important that all the main evidence should be published. It is a pleasure to record our thanks to the many officers, named and unnamed, who have devoted so much time, thought and care in an attempt to place our knowledge about the prevention and treatment of wound infection on a more secure basis.

THE RESULTS RELATED TO THE AGENTS EMPLOYED

The main problem was to discover the best adjuvant to good surgery in order to secure the highest degree of success in delayed primary and secondary wound sutures. It was stipulated that, apart from the chemotherapeutic agents employed, every other factor such as surgery, rest, nursing, diet, etc., should be of the same standard in all cases, with no preferential treatment for any one group. The cases were to be consecutive, unselected wounds of the soft tissues, and alternate cases were to be treated:—

(*a*) With penicillin and

(*b*) With a contrast agent.

* Two of the published reports arrived too late to be used in compiling the tables in this consolidated report. Rough calculations show, however, that the figures produce no significant variations in the results.

The idea was that the surgeons would select for contrast agents those generally regarded as the best alternatives to penicillin, and it was expected that several thousand results would be available for analysis, providing a representative cross section of the wounds treated by many surgeons. This last is a very important point, since so many published reports deal with relatively small groups of cases which received preferential treatment (*e.g.*, being held in hospital for longer periods than usual) or which were perhaps operated upon by someone above the average in surgical skill.

Theoretically, the groups should be almost equal. In fact they are not. This is because so many surgeons became convinced at a relatively early stage of the superiority of penicillin and abandoned the use of contrast agents.

The assessment employed and other details of the scheme are given in the explanatory notes on "An Investigation into the Prophylaxis and Treatment of Wound Infections". (Chap. II Pg.7).

The overall results are summarised in Table I.

RESULTS OF WOUND SUTURES IN 4432 CASES USING VARIOUS ACENTS

TABLE I

Agents used	Total cases	Grade I		Grade II		Grade III		Per-centg. Grades IandII
		Number	per cent	Number	per cent	Number	per cent	
Penicillin — local applications only	2359	1881	79.73	348	14.75	130	5.52	94.48
Penicillin — local and parenteral	1485	1221	82.22	185	12.46	79	5.32	94.68
Penicillin — parenteral only	107	92	85.98	12	11.21	3	2.81	97.19
"Nuflav" (local application)	137	80	58.39	33	24.09	24	17.52	82.48
Sulphonamides — local and systemic	141	88	62.41	30	21.27	23	16.32	83.68
Sulphathiazole — 1 per cent Proflavine (local)	46	19	41.30	18	39.13	9	19.57	80.43
Nil	157	114	72.61	25	15.92	18	11.47	88.53

The results may be shown more simply by contrasting the penicillin cases with all the others (Table II).

SUMMARY OF RESULTS IN TABLE I

TABLE II

Agents	Total cases	Grade I		Grade II		Grade III		Per-centg. IandII
		Number	per cent	Number	per cent	Number	per cent	
Penicillin	3951	3194	80.84	545	13.79	212	5.37	94.63
Others	481	301	62.57	106	22.04	74	15.39	84.61

These tables are top heavy because, for the reason already given, the penicillin cases outnumber the others by about 8 to 1. This renders direct comparison less easy, and some of the groups are so small that the range of possible statistical error is high. Despite this, the result is definite, and in this large series of cases operated upon by so many different surgeons the penicillin cases did better than the others. This is more evident if one selects the highest standard (Grade I—complete healing within fourteen days) as the criterion of success; and it is interesting to observe how, by lowering the standard and including both Grades I and II (*i.e.*, all wounds completely healed within twenty-one days) the differences become less evident.

The results in the group receiving no local or general therapy will attract attention, but they cannot be compared strictly with the others as this group contains no major cases. It represents what can be accomplished by unaided surgery in small clean wounds. And it must be remembered that the majority of these patients had prophylactic penicillin or sulphonamides before admission to the hospital where suture was performed.

On the other hand the penicillin groups, and particularly those receiving parenteral penicillin, contain practically all the major wounds, yet these show the highest degree of success whatever standard is adopted. Viewed in the light of this knowledge the penicillin results appear still better.

It has been emphasised that all controllable factors were standardised as far as is possible in a clinical investigation, and in large series of cases wounds of every part, type and degree of severity are represented. Therefore these variables are not considered separately, as it is believed the numbers are sufficiently great to minimise or equalise their effects. Incidentally where figures are supplied about some of these factors, *e.g.*, size of wounds, it is apparent that they produce no significant difference in the results (see Table V in Lt.-Col. A. G. R. Lowdon's report).

About some factors, however, there is divergence of opinion and these deserve further analysis.

TIME INTERVALS

Individual reports show variations in opinion regarding the effects of increasing time intervals between wounding and operation. This factor is analysed in Table III. All cases included in this table were treated with penicillin, and the first column represents the interval following wounding within which suture was performed

THE EFFECTS OF INCREASING TIME INTERVALS (PENICILLIN CASES)

TABLE III

Days between wounding and suture	Total Cases	Grade I		Grade II		Grade III		Per-cent Grades I and II
		Number	per cent	Number	per cent	Number	per cent	
1 — 7 days	892	789	88.45	66	7.40	37	4.15	95.85
8 — 14 days	397	324	81.61	51	12.85	22	5.54	94.46
15 — 21 days	92	64	69.56	17	18.48	11	11.96	88.04
Over 21 days	20	11	55.00	7	35.00	2	10.00	90.00

The last group is too small to be of much significance. In the others it is seen that the percentage of Grade I successes falls as the time intervals lengthen. If Grades I and II are both included the differences become less apparent (see last column). This is shown in a larger series of cases in Table IV. It includes the figures in Table III plus figures added from reports in which the Grade I and II results were not differentiated. By comparison with the Grade I column in Table III it reveals how clear cut decisions may be obscured by too broad divisions.

THE EFFECTS OF INCREASING TIME INTERVALS

TABLE IV

Days between wounding and suture	Total Cases	Grades I and II		Grade III	
		Number	per cent	Number	per cent
1 — 7 days	1290	1236	95.81	54	4.19
8 — 14 days	667	627	94.01	40	5.99
15 — 21 days	148	133	89.86	15	10.14
Over 21 days	48	43	89.58	5	10.42

Except in the case of "Nuflav" the figures about time intervals are not given for the contrast agents, or the numbers are too small to be worth recording. Even the "Nuflav" series is not large, but it is given below:

THE EFFECTS OF INCREASING TIME INTERVALS ("NUFLAV" CASES)

TABLE V

Days between wounding and suture	Total cases	Grades I and II		Grade III	
		Number	per cent	Number	per cent
1 to 7 days	39	36	92.31	3	7.69
8 to 14 days	42	33	78.57	9	21.43
15 to 21 days	19	11	57.89	8	42.11

These figures are suggestive but not conclusive in view of the small numbers. Where it is possible to separate Grades I and II the differences become still more marked, and strongly favour the view that increasing time intervals diminish the chances of successful suture. These figures are not given separately as the numbers are small and in consequence may be misleading.

Several surgeons discuss the time factor and point out that longer intervals mean more granulation tissue, fibrosis, loss of elasticity in the wound margins, and a greater liability to infection. At operation these necessitate more excision and undercutting with increased risk of haematoma formation and infection, and possibly increased tension following suture.

The time interval between wounding and primary surgery is co-related with the degree of infection and the results of suture in Table III of Lt.-Col. J. C. Anderson's report. In his next table the same officer shows that delayed primary suture performed on the third day after primary surgery appears to offer the highest chance of success; in the majority this is the third of fourth day after the wound was sustained.

THE EFFECTS OF EXCISION ON THE RESULTS

Excision may be necessary at two stages: (*a*) at the primary operation and (*b*) before suture: —

(*a*) The importance of the former has been stressed elsewhere in this brochure, and all surgeons agree that wounds treated by adequate primary surgery are usually ready for suture when first seen in hospital. Lt.-Col. A. G. R. Lowdon shows the results of wound suture related to previous surgery in 808 wounds (Table VII), and he points out that although the difference between the two groups is not significant, the wounds operated upon by forward surgeons can be sutured more easily and at an earlier period than those not previously treated.

Many surgeons do not excise clean wounds produced by bullets. Lt.-Col. J. W. Bridge thinks this is a mistake, and other surgeons share this belief. He gives the following results in thirty-four cases of this type;

16 G. S. Ws. No primary excision; twelve (75 per cent) healed within twenty-one days following delayed primary or secondary suture.

18 G. S. Ws. Primary excision within first week; seventeen cases (94.4 per cent) healed within 21 days following delayed primary or secondary suture.

(*b*) Most surgeons believe that a variable degree of excision is desirable at the time suture is performed. This is a difficult factor to assess as it is bound up closely with others such as

the clinical state of the wound, time intervals, etc. The available figures are tabulated below. They all refer to cases treated with penicillin.

RESULTS OF SUTURES WITH AND WITHOUT EXCISION

TABLE VI

Method	Total Cases	Grade I		Grade II		Grade III		Percentage Grades I and II
		Number	per cent	Number	per cent	Number	per cent	
Excision	236	186	78.81	34	14.41	16	6.78	93.22
No Excision	43	31	72.09	10	23.26	2	4.66	95.35

Again we have a top heavy table, but the figures tend to support the idea that the chance of Grade I healing is enhanced by excision. This effect may be greater than the figures reveal, since most of the wounds not requiring at least partial excision were of a minor character. But when Grades I and II are both regarded as successes the margin between the groups becomes narrow (2.13 per cent) and of no significance. This is shown in larger groups in Table VII, which includes those in Table VI plus figures from reports in which Grade I and II results were recorded together.

RESULTS OF SUTURES WITH AND WITHOUT EXCISION

TABLE VII

Method	Total Cases	Grades I and II		Grade III	
		Number	per cent	Number	per cent
Excision	714	673	94.25	41	5.75
No Excision	123	114	92.68	9	7.32

The margin of difference between the Grade I and II results in these larger groups is of no significance (1.57 per cent).

RESULTS RELATED TO CONDITION OF WOUND BEFORE SUTURE

Wounds that in pre-penicillin days would have been considered quite unsuitable for suture are now closed regularly and with impunity. This is one of the most notable advances achieved during this war, and has brought many benefits to the patients in the prevention of pain, in providing better cosmetic and functional results, in avoiding prolonged suppuration with consequent visceral damage, and in shortening convalescence. This one advance in itself must have saved many limbs and even lives. The success led to one curious result. Men who thought they had collected "blighty" wounds found themselves instead in convalescent depots with completely healed

wounds within 3–4 weeks of being hit, and while the physical result was excellent the psychological response was poor. This problem assumed such importance that the Director of Medical Services, 21 Army Group, introduced a rule that any battle casualty who had been in a hospital or convalescent depot for a month after wounding should invariably be granted a week's sick leave in the U. K. This wise decision solved the difficulty.

There has only been one serious complication* following many thousands of sutures in this theatre — a case of gas gangrene — although many closures were performed in frankly infected wounds or in those requiring extensive excisions of devitalised tissues or foreign materials. The methods employed approximated closely to those described in the "Memorandum on Penicillin Therapy in 21 Army Group" and need not be repeated here.

The term clean is employed in a clinical and not a bacteriological sense. It means wounds showing only mild evidences of inflammation inseparable from any injury and with minimal discharge and contamination, but not necessarily sterile. Many in fact contained pathogenic organisms, and these were doubtless held in check and finally eliminated by the combined effects of the normal body defences and penicillin. The dirty wounds were more or less purulent, often with tags of devitalised tissue and well formed granulations, and sometimes containing foreign material.

The next table compares the results following suture in the two classes of wounds.

RESULTS RELATED TO CONDITION OF WOUND BEFORE SUTURE

TABLE VIII

Condition of wound	Total Cases	Grade I		Grade II		Grade III		Percentage Grades IandII
		Number	per cent	Number	per cent	Number	per cent	
Clean	760	612	80.53	107	14.08	41	5.39	94.61
Dirty	117	80	68.38	24	20.51	13	11.11	88.8

The difference in results is significant, especially if Grade I healing is regarded as the standard. The result is just what would be expected, yet it is interesting to note that about 89 per cent of unclean wounds were completely healed within twenty-one days following suture. Only a few years ago no sensible surgeon would have considered closing most of them.

Preoperative prophylactic chemotherapy has an influence on the condition of the wounds as can by seen by referring to various tables in the individual reports, and to the consolidated figures in the

* Footnote: Since this was written we have heard of another similar case (see Lt. Col. E.A. Jack's report).

article on "Penicillin and Sulphonamides in Prophylaxis". Several surgeons correlate this preoperative treatment with the results obtained following suture (vide *e.g.*, Table XI, in Lt.-Col. A. G. R. Lowdon's report, Table V in Lt. Col. R. L. Holts report and Table II in Lt. Col. J. C. Andersons's report). In effect the conclusion to be drawn from these tables is that the chances of success are slightly higher if oral sulphonamide is given in addition to penicillin. However, as the results with penicillin alone are so good, it is doubtful if any slight increase in the success justifies the coincident use of a drug that occasionally produces annoying and even dangerous complications.

RESULTS RELATED TO SITE OF WOUNDS

Wounds in different areas heal at varying rates as is well known. Table IX shows the results in 878 wounds of various parts of the body, and it is evident the advent of penicillin necessitates no alterations in previous concepts on this aspect.

RESULTS RELATED TO SITE OF WOUNDS

TABLE IX

Site	Total Cases	Grades I and II	Grades III	Percentage Grades I and II
Head and Neck	38	38	—	100.00
Upper Extremity	177	171	6	96.61
Trunk	130	123	7	94.62
Buttock	68	64	4	94.12
Lower Extremity	465	427	38	91.83
Totals	878	823	55	93.74

The rate of healing in different areas falls slowly from above downwards, and the difference becomes more evident if the leg and foot are considered separately. Figures for these sites are available in several reports:—

Leg and Foot 116 wounds. Grade I and II results following delayed primary or secondary suture ninety-nine (85.34 per cent).

PRESENCE OF FOREIGN MATERIAL

It has been suggested that the existence of foreign material in a wound when a patient reaches hospital is an indication of inadequate primary surgery. If this were qualified by adding the adjective "obvious" it would be true, but many foreign bodies removed at the

secondary operation were buried metallic fragments, and their continued presence may often be regarded as evidence of wisdom on the part of some forward surgeon who refrained from blind explorations in the absence of facilities for accurate localisation.

Several cases are mentioned later in which the non-removal of foreign material led to failure. But does the removal of a foreign body at the time of operation for closure influence the result? Table X shows the results in 194 wounds.

RESULTS FOLLOWING REMOVAL OF FOREIGN BODY AT TIME OF CLOSURE OF WOUND

TABLE X

	Total Cases	Grade I		Grade II		Grade III		Percentage Grades I and II
		Number	per cent	Number	per cent	Number	per cent	
F. B. removed	93	71	76.34	13	13.98	9	9.68	90.32
No F. B. removed	201	143	71.14	42	20.90	16	7.96	92.04

The presence of a foreign body and its removal at the operation for closure seems to produce no significant difference in the results.

RESULTS RELATED TO EXPERIENCE OF SURGEON

The less experienced surgeons operate upon the less serious cases, and this fact is reflected in the results in Table XI. Given such cases Jack is as good as his master. From the figures available it is impossible to separate Grades I and II in all cases, so these are given together.

RESULTS RELATED TO SURGICAL EXPERIENCE

TABLE XI

Surgeon	Total Cases	Grades I and II		Grade III	
		Number	per cent	Number	percent
More experienced	870	826	94.94	44	5.06
Less experienced	353	331	93.77	22	6.23

BACTERIOLOGY OF WOUNDS

With few exceptions all reports state that routine bacteriological investigation of wounds is unnecessary, and that as regards wound closure it offers little help either in deciding treatment or prognosis. Army hospital laboratories are understaffed in comparison with civilian hospitals of the same size, and additions to their work should be avoided unless some very definite advantage is gained. The extra work may be heavy, as during peak periods some surgical teams were performing thirty to forty wound closures a day. The surgeons made their decisions on clinical grounds, the best guide, and if they had awaited the results of full laboratory tests the operation would have

been delayed two or three days. Thus the bacteriological findings arrive after the operations have been performed, except in those cases where the infection is more severe and where in any case the surgeon would decide against operation on clinical grounds. The figures obtained merely show so many wounds contain this and so many others contain that pathogen, but this is knowledge of no great practical value and merely adds wood to the pile of established facts. In the days when every unit of penicillin was important investigation of each case was essential to avoid wasting the precious substance, but these days have now passed.

If the clinical and bacteriological results invariably coincided the case in favour of routine cultures would be stronger, but anyone with experience knows they do not always agree. They sometimes pursue an independent or contrary course even when the greatest care is taken in the collection of samples, the cultures, and the interpretation of results. In not a few cases if one studied consecutive bacteriological reports alone, one might easily imagine the condition was deteriorating, whereas in fact the reverse may be true. With highly specialised techniques these discrepancies could doubtless be eliminated, but the average army pathologist lacks the time, facilities and possibly the experience to carry out such investigations.

While the great majority believe that routine cultures before suture are a needless waste of time for all concerned, most believe that more information might be gained by devoting intensive study to a smaller number of cases, or by concentrating on the failures and attempting to discover any common factor or factors producing them. Study of the report submitted by Young, Evans and Hughes will reveal that such investigations may prove more fruitful in adding to our knowledge.

The following list gives the distribution of the organisms isolated at the first examination after admission to hospital in 560 wounds. The majority had been treated with penicillin although the exact proportion cannot be discovered, and it must be stated that penicillinase was not employed in many of the cultures. We do not know if anaerobic cultures were always performed.

Staphylococci, Coagulase +	62
Staphylococci, Coagulase —	26
Staphylococci, no details given	51
"Coliforms"	56
Streptococci haem.	18
Streptococci anhaem.	11
Diphtheroids	22
"Micrococci"	19
Proteus	9
Clostridia	9
Enterococci	4
B. subtilis	3
Ps. pyocyaneus	2
No growth obtained	268

It will be noted that staphylococci were much the commonest organisms, occurring in 139 wounds, whereas streptococci were only isolated from twenty-nine. Of penicillin - insensitive types those belonging to the coliform group were most common. Needless to say many wounds gave mixed growths, and it will be clear from the figures that many cultures were sterile, but we cannot be certain how many false negatives resulted from penicillin carried over on the swabs or loop.

FAILURES

Many causes of failure have been mentioned in the individual reports and these will be summarised.

INFECTION. This was noted as the chief or contributory cause of failure in at least forty-seven cases. The principal offending pathogens were.

Coliforms	23
Staphylococci (coag + and pen. sensitive) ...	4
Staphylococci (coag + and relatively pen. insensitive)	3
Staphylococci (Details unknown)	14
Ps. Pyocyaneus	9
Streptococcus	6
Proteus	4
Cl. welchii	2
Enterococci	1

These occurred alone or in combination, and it will be seen that coliforms (twenty-three) and staphylococci (twenty-one) are most frequently implicated and are presumably of most importance. It will be noted that the only pathogen occurring more frequently than at the primary bacteriological examinations was Ps. pyocyaneus.

A number of failures were due to sepsis in underlying structures (osteomyelitis, sloughing fascia or tendons, etc.).

TENSION. This was mentioned as the chief cause of failure in twenty-eight cases, and as a contributory cause in others.

Lt.-Col. A. G. R. Lowdon shows the results related to the degree of tension in Table XI of his report. Allowing for possible statistical error the surprising thing is the small margin of difference between wounds sutured under minimal and maximal tension.

This factor, however, is regarded by most surgeons as one of the most important causes of failure.

TIME. The effects of increasing the intervals in predisposing to failure have been demonstrated in Tables III, IV and V.

INADEQUATE PRIMARY SURGERY. This factor has also been discussed. Sometimes the initial efforts are over-adequate. In four cases the failure was attributed to undue tension on the sutures following excessive excision of skin by forward surgeons.

INADEQUATE SECONDARY SURGERY. Somewhat naturally this is seldom implicated. Two surgeons admit to failures following the use of badly designed flaps, three failures were attributed to inadequate excision, in two haematoma formation due to inadequate haemostasis is mentioned, and in three the non-removal of small pieces of cloth undiscovered at the time the wound was closed led to subsequent breakdown.

Table VII gives the results in wounds treated by excision compared with those that were not, and while the end results were similar, it is probable that the excised wounds healed more rapidly.

FOREIGN MATERIAL. This factor is bound up to some extent with the adequacy of the surgery. Foreign bodies are given as the cause of failure in fifteen cases. In seven of these pieces of cloth were present, in four fragments of phosphorous, and in one buried catgut. In the others pieces of metal alone were responsible. Obviously it is desirable to remove dangerous or irritating foreign material.

The results obtained following removal of a F. B. at the time of operation are shown in Table X.

In six cases it is stated that sutures were performed with no attempt made at removing buried metallic fragments and all these wounds healed by first intention.

EXPERIENCE OF SURGEON. This must be of importance, but in practice is masked by the fact that the more experienced surgeons tackle the more severe wounds. This is shown in Table XI.

TENTAGE OR POCKETING. These are more liable to occur in the more severe wounds, and are dealt with by the more experienced surgeons. This may explain why these factors are given as a cause ot failure in only six cases.

UNFAVOURABLE SITE. This was stated to be the chief or contributory cause of failure in twenty-seven cases (seven buttock, four back, three over scapula, two axilla, four over tibia, two dorsum of foot, two dorsum of hand, one perineum, one dorsum of finger and one over spinous process of vertebra). In the back and buttock areas mechanical and physical factors play a part — pressure, movement, lack of ventilation, etc.

TYPE OF WOUND. In nine cases failure was attributed to the gross size and extensive degree of tissue damage and laceration. In five cases cruciate or T-shaped wounds broke down slightly at the centre, and in three a bridge of undermined skin between two wounds sloughed owing to interference with its blood supply.

PREVIOUS LOCAL TREATMENT. Several surgeons mention that excessive use of soft paraffin or voluminous dressings interferes with ventilation and evaporation and produces "soggy" wounds. These are less favourable for suture.

LACK OF REST. Absence of immobilisation was blamed for failure in three cases. In five others too early transfer following

suture was regarded as the possible cause. Most surgeons agree that transfer is undesirable within four to five days following suture unless the move is dictated by tactical considerations.

TO SUMMARISE. The most common causes of failure cited by surgeons are infection, undue tension, an unfavourable site, and the presence of irritating foreign material. The other factors detailed above are implicated less frequently, and failure is more often due to a combination of unfavourable factors rather than to a solitary cause.

OPEN BONE AND JOINT INJURIES

Several reports include cases of open bone and joint injuries, and we are indebted to Lt.-Col. A. L. Eyre-Brook, Adviser in Orthopaedics, and Lt.-Col. McNaughton, Officer i/c Surgial Division, 20 Canadian General Hospital, for information about others. We have figures for 188 compound fractures and seventy-seven penetrating wounds of the knee joint. Amongst the fractures forty-four involved the femur; the exact distribution of the remainder is unknown. In twenty of the femoral cases open reduction was performed and fixation secured by screws or wires, and several had bone grafts in addition for the replacement of bone defects. Only four of the forty-four femoral cases were unhealed after three weeks, and two of these were in the group of patients who had had open reduction and fixation. The majority of the wounds healed as perfectly as after a clean orthopaedic operation, although some were originally extensive and associated with much bone and tissue damage. In at least three cases (two tibiae and one scapula) closure was effected with the aid of sliding flaps, and one of these was unhealed at three weeks; in this case the surgeon blamed himself for a badly designed flap.

The total results were as follows:—

RESULTS OF CLOSING WOUNDS IN OPEN BONE AND JOINT INJURIES WITH AID OF PENICILLIN

TABLE XII

Type of Wound	Total Cases	Grades I and II		Grade III	
		Number	per cent	Number	per cent
Open bone injury	188	173	92.02	15	7.98
Open joint injury	77	73	94.81	4	5.19
Totals	265	246	92.83	19	7.17

These results resemble those obtained in uncomplicated soft tissue wounds, but they must be studied in the knowledge that:—

(*a*) unlike the soft tissue wound results reported above, these were selected and not consecutive cases; and

(*b*) in the majority the follow-up did not exceed one month, as men likely to require more prolonged hospitalisation were evacuated to the U.K.

These figures show, however, that if suture of a wound over a bone or joint lesion is mechanically possible, with the aid of penicillin a very high standard of success is attainable. Unfortunately they cannot be accepted as final figures since wounds associated with bone injuries are notorious for late break-downs. We know this has occurred in one series of bone grafts (cancellous) for mandibular defects performed at an early stage following wounding in one of the special maxillo-facial units in this theatre. Complete initial healing was obtained, yet some of these broke down as long as two months after the operation. This is no condemnation of the method or the surgery, as the patients are all much better off now than if they had not been operated upon. All surgeons accept the view that early closure of wounds offers great advantages, and soon the idea will prevail that early replacement of bone defects is no less important.

SUMMARY

1. The results of wound closure using penicillin and other agents are compared.
2. It is shown that, on equal terms, penicillin is superior to all other agents available. The difference is most evident if the highest standard of healing is adopted as the standard of comparison.
3. The chances of success diminish progressively with increasing time intervals between wounding and suture.
4. The optimum time for suturing war wounds is 3–4 days after wounding.
5. Adequate primary surgery facilitates early closure of wounds.
6. Meticulous and careful excision performed before closure leads to earlier and better healing.
7. The differences that might be produced by variations in surgical experience are masked by the fact that the more severe wounds are treated by the more experienced surgeons, and vice versa.
8. Infected wounds can be sutured with safety unless the degree of infection in serious, and with the aid of penicillin a high degree of success is attainable even in dirty wounds.
9. The decision to operate is best based on clinical judgment and routine bacteriological investigations, with consequent delays, are unnecessary in the majority of cases.
10. The most common penicillin-sensitive pathogen in wounds sustained in this theatre has been the staphylococcus. The most common penicillin-insensitive organisms have been coliforms.
11. The commonest causes of failure are infection, tension, an unfavourable site, or the presence of irritating foreign material. Failures are often due to a combination of causes rather than to one solitary factor.
12. In open bone and joint injuries if closure is mechanically possible the results approximate closely to those obtained in uncomplicated soft tissue wounds.

INTENSIVE INTRAVENOUS PENICILLIN THERAPY

A report on 100 consecutive cases treated by this method.

By Lt.-Col. Seymour Heatley, RAMC., Officer i/c Surgial Division,
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The possible value of intensive penicillin therapy was suggested by two articles, one by Bigger (1944)(1), and the other by Fleming (1944)(2). Bigger showed that penicillin is bactericidal rather than bacteriostatic if used in adequate dosage, and he suggested a scheme of intermittent sterilisation to exploit this property clinically. Fleming and his co-workers showed how it was possible to obtain high serum levels very easily by frequently repeated intravenous or intramuscular injections, and it was decided to combine the two ideas and study the results. Bigger's "hypothesis to explain why such an apparently active bactericidal substance frequently fails to sterilize suspensions of susceptible microorganisms" appeared attractive, and made it seem of interest to investigate the effects of intensive intravenous penicillin therapy in a series of cases of staphylococcal and other infections occuring in the human body.

It was hoped that by the introduction of large doses of penicillin into the blood stream at frequent intervals a sufficiently high level of penicillin could be maintained in the patient's serum, and more important in the tissues which may have a poor blood supply, to kill off large numbers of staphylococci quickly, and that the normal defences of the body would complete the destruction of the remaining organisms.

Owing to the fact that the investigation was undertaken at a time when the hospital was particularly busy, it was impossible to exercise anything like adequate serological or bacteriological control, and the results obtained were judged purely on clinical findings. Major K. E. A. Hughes, RAMC found time to estimate the amount of penicillin in the blood in a number of cases*, and from these one or two observations can be made :—

(*a*) A sufficiently high penicillin level in the blood stream to kill off bacteria could be achieved and maintained.

(*b*) A high level of penicillin in the patient's serum did not necessarily mean a good clinical reponse, and conversely good

*Ed. Footnote: See next report.

results were obtained in patients when a high level in the serum was neither reached nor maintained.

(c) Penicillin was quite definitely found in pus from the peritoneal cavity in two cases.

TECHNIQUE

The preparation and administration of penicillin calls for a high degree of skill and care. Two RAMC orderlies were instructed in and entrusted with the maintenance and sterilization of the giving sets, and two sisters selected to administer the correct doses, ensure an even flow of saline into the vein, and to see that the needle did not become blocked or disturbed in any way.

The standard army intravenous saline giving set was used, slightly modified in that a small piece of rubber tubing and a glass connection were inserted between the intravenous needle and the long tube leading from the drip-counter. Through this piece of rubber tubing the penicillin was injected by a hypodermic needle, and the glass connection permitted observation of the flow of blood when the vein was entered. The patient's arm was bandaged to a splint, a needle introduced and fixed securely in a vein, and saline run in at the rate of ten drops per minute. Ten seconds before injection of penicillin the rate of flow of saline was increased to forty drops per minute and this rate maintained for a minute after the administration of the penicillin. In this way 20,000 units were introduced every fifteen minutes until the desired dosage had been attained. The average total amount administered by this method was 300,000 units, but some severe cases had as much as 750,000 units at one treatment.

In the hands of the sisters specially trained for this work no technical difficulties whatever were encountered nor was there a single instance of thrombosis of a vein, but two patients did complain of a little stiffness in the arm for twenty-four hours. In a series of cases treated in other wards (not included in this report) where strict attention to detail was not observed several cases of thrombosis did occur.

Although the results obtained with this technique were extremely good is was noticed that in our first twenty-five cases there were four relapses, one in Group I and three in Group III (see below). It was thought possible that these relapses could be explained by the presence of the "persisters" described by Bigger. Our technique was modified subsequently. In addition to the desired amount of intravenous penicillin, an intramuscular drip was set up simultaneously and 100,000 units in twenty-four hours were given by this method for two or three days depending on the severity of the case. Since the adoption of this modification no relapses have been observed.

SUMMARY OF CASES SELECTED FOR TREATMENT

I.	Carbuncles	20
II.	Severe infections of the hand	15
III.	Lymphangitis	16
IV.	Grossly infected wounds of the soft tissue	42
V.	Acute abdomens	5
VI.	Chronic Osteomyelitis	2

The above table comprises 100 consecutive cases treated in my own wards. A considerable number of cases have been similarly treated by other members of the staff of this hospital, who report equally favourable results.

GROUP I — CARBUNCLES

Of these cases ten were carbuncles of the forearm and ten of the face or neck. All were severe infections and had been subjected to various forms of dressings, antiseptics, etc., with deplorable results. The average time between the conset of the infection and the beginning of penicillin treatment was nine and a half days. In less than four hours the improvement in their general condition was quite remarkable; pain had disappeared, the temperature and pulse became normal, the oedema surrounding the infection decreased, and movement of the head or arms and hands became possible and comfortable. In all cases the patients themselves were surprised at the improvement in their condition in such a short time.

Within three days the slough separated leaving a clean, healthy, granulating wound, which, where necessary, was skin grafted on the following day. All the grafts were successful and every patient was returned to his unit fit for full duties in less than twenty-one days from the day of admission. It may be worth while recording that in infections of the face the end result was so good that very little, if any, scarring could be detected. There was one failure and one relapse in this series. The pus from the first case grew a pure culture of bacillus coli, and the relapse was a carbuncle of the face which responded to a second course of treatment.

GROUP II — INFECTED HANDS

Here again only the most severe infections of the hands and fingers were chosen. Seven cases were distal space infections of the fingers and thumb, and eight of the mid-palmar space. After incision to allow adequate drainage, intensive therapy was administered with gratifying results. The infection subsided extremely quickly, the patient regaining good movements of the hands and fingers almost at once, and as this is the most important factor in preventing subsequent stiffness, it, in my opinion, justifies the adoption of this

form of therapy for severe infections of the hand. All patients except one were fit to return to their units in fourteen days. The remaining patient, a Canadian sapper who had been building Bailey bridges, could not be spared from his work, and was not seen until twelve days after the onset of a mid-palmar space infection. On admission to hospital he was extremely ill and suffering from the most severe infection of its kind that I have seen in twenty years, but in spite of this the treatment was so successful that he left hospital on the 26th. day with full movements of all fingers.

GROUP III — LYMPHANGITIS AND LYMPHADENITIS.

In these cases the results of treatment were not so dramatic as in the previous groups and there was a tendency to relapse, necessitating much larger doses and for longer periods. It would appear that penicillin cannot deal so effectively with the streptococcus as it can with the staphylococcus; or that we were seeing here, what Garrod (1945) [3] had suggested was possible, that a high concentration of penicillin may be less effective than lower levels in certain infections.

Three patients in this series were apparently cured by the administration of 300,000 units in 3¾ hours. The temperature and pulse dropped to normal and the red lines on the patients' arms disappeared, but forty-eight hours later the condition recurred. Two responded immediately to a second course. The third required a further 250,000 units.

Case History — Cpl. "S" Age 22; 2/*Gordon Highlanders.*

14. 2. 45 Admitted suffering from severe lymphangitis of the forearm and arm. Large brawny swelling of the medial site of the arm with considerable enlargement of the axillary glands. T. 103° F; P. 106: R. 22.

15. 2. 45 300,000 units penicillin given in 3¾ hours.

16. 2. 45 Apparently cured. Temperature, pulse and respirations normal.

17. 2. 45 Allowed up — feeling very well.

18. 2. 45 Relapse. Condition very similar to that on the day of admission. T. 103° F; P. 100; R. 20. 300,000 units penicillin.

19. 2. 45 Again apparently cured.

21. 2. 45 Allowed up.

23. 2. 45 Further relapse. T.103° F; P. 90: R. 20. Penicillin 250,000 units intravenously, followed by 150,000 units by intramuscular drip during the next thirty-six hours.

27. 2. 45 Finally cured.

COMMENT: This case is of interest as on two occasions his condition was apparently cured and recurred after forty-eight hours. It is possible that, on clinical grounds, this case together with the two patients mentioned above, and the relapse described in Group I

afford definite confirmation of Bigger's hypothesis of the pr sence of "persisters". It was the experi nce that we gained from these three cases that led us to modify our technique.

GROUP IV — GROSSLY INFECTED WOUNDS OF THE SOFT TISSUE.

This group consisted of forty-two severely infected wounds of soft tissue, which during busy periods in the forward areas arrived at this hospital without the benefit of early surgical treatment. In all cases there was gross infection of the wound, inflammation of the surrounding tissue, and a copious discharge of pus. Eighteen we e caused by high explosive shell and twenty-four by mortar bombs. The average time between the date of wounding and operative treatment in this hospital was six and a half days.

Previous experience of penicillin therapy in soft tissue wounds had shown that there are three main causes why such wounds fail to heal: —

(a) All necrotic muscle, and muscle tissue with a negligible blood supply, must be radically removed. If this is not done parenteral penicillin will not reach infected tisssue and failure must result. This is easily seen in the treatment of simple through and through bullet wounds; those which are excised and treated with penicillin are all well healed within eight days, whereas similar wounds treated by penicillin alone generally require three weeks before the patient can be returned to his unit.

(b) Foreign bodies, and in particular irregular shaped fragments which so often carry clothing and other infected material into the tissue, must be removed.

(c) There must not be undue tension on the skin margins when the wound is closed.

If these three principles are observed more than ninety-five per cent of all soft tissue wounds will heal well if the operation is followed by the administration of penicillin by continuous intramuscular drip.

At first sight, therefore, it would appear that intensive intravenous therapy is unnecessary in soft tissue wounds, but the group of cases under review were grossly infected and were operated on six-and half days after wounding. It was felt that the risk of opening up fresh tissue and thus spreading infection was considerable, unless the maximum amount of parenteral penicillin could be brough into contact with the operation field in the shortest possible time. Under the protection of intensive intravenous therapy complete excision of the infected area was carried out and the resulting wound sutured (three sutures to the inch in order to permit the escape of pus or serum). Intravenous plus intramuscular therapy was given for three days after operation.

RESULTS

Thirty-five of the forty-two cases (eighty-three per cent) were soundly healed on the eighth day when the sutures were removed. In six cases where there was either undue tension on the skin edges, or where accurate apposition could not be obtained at operation owing to skin loss, the wounds had not completely healed and were therefore grafted on the ninth day after operation. Five of the six grafts were successful: the sixth case was evacuated before being examined and the final result had not been ascertained.

One case, a penetrating wound of the neck, grossly infected on admission, was a complete failure in spite of two courses of treatment, and was evacuated to the United Kingdom owing to pressure on bed space.

GROUP V — ACUTE ABDOMENS

(*a*) *Appendicular Abscesses.* Three cases had not been operated on, and the fourth case developed a pelvic abscess three days after appendicectomy. Here again, approximately three hours after the commencement of intensive intravenous treatment, the patients' temperatures and pulses dropped to normal, and the abscesses decreased rapidly in size. The patients were able to enjoy full diet, there was no return of the pain, nausea or vomiting, and they were all evacuated to the United Kingdom within seven days.

(*b*) *Acute Cholecystitis.* This case occurred in an officer who had been a prisoner of war for four years. On admission to hospital he was gravely ill with a temperature of 103.8^{o} F. and a pulse of 140 with severe abdominal pain. There was history of two previous similar but less severe attacks. On examination an extremely large gall bladder could be felt. Within four hours of the commencement of treatment his temperature and pulse had returned to normal, where they remained, pain had disappeared, and the patient's appetite returned and he was able to take normal food. As he was evacuated to the United Kingdom his further progress cannot be recorded.

COMMENT: Penicillin has been found in pus from the peritoneal cavity. It is not suggested that it has any effect on bacillus coli, which is comparatively harmless. It has a very definite action on the other organisms present.

GROUP VI — CHRONIC OSTEOMYELITIS

Both patients were Officers of the Belgian Army, wounded in 1940, and suffering from chronic osteomyelitis of the tibia. After sequestrectomy they were given two courses of penicillin therapy.

Both were failures. In one case examination of the pus revealed the infection was due to bacillus coli; in the other bone sclerosis prevented penicillin reaching the invading organisms.

CONCLUSION

It must be admitted that conclusions based on clinical observations only are unsatisfactory.

A comparable series of cases will be investigated in the near future, with similar methods of treatment and with complete serological and bacteriological control.

Experience gained by the treatment of this series of cases may permit the following observations:

1. Intravenous administration of penicillin by the methods described has definite advantages over other current methods.
   - (*a*) In selected cases, the rapid attainment of a high penicillin level in the blood serum may prove a life-saving factor.
   - (*b*) The marked inprovement in the patient's general and local condition within a few hours of the commencement of treatment is striking.
   - (*c*) The time saved in the administration of penicillin by this method (e.g. 600,000 units given by ordinary drip takes six days: in intensive therapy the same amount can be given in $2\frac{1}{4}$ hours each day on three successive days, with equally good or better results) is a distinct advantage to the patient in that it permits early active movements and physiotherapy, and obviates stiffness of the leg which is apt to follow prolonged intramuscular therapy.
2. There is considerable evidence that penicillin administered in large and frequent doses is bactericidal in action.
3. There is clinical evidence to support Bigger's hypothesis of the existence of "persisters".

I acknowledge with gratitude the help I have received from Capt. (Miss) I.M. Bower, RAMC, Miss K.W. Emerson, QAIMNS, and Ptes. Ward and Williams, RAMC.

REFERENCES:

(1) Bigger J. W. (1944), Lancet, II, 497.

(2) Fleming, A., Young, M. V., Suchet, J., and Rowe, A. J. E. (1944), Lancet, II, 622.

(3) Garrod L. P. (1945), Brit. Med. J., I, 107.

INTENSIVE INTRAVENOUS THERAPY

By Major K. E. A. Hughes, RAMC, O.C. No. 3 Mobile Bacteriological Laboratory.

In connection with the clinical trial of intensive intravenous penicillin therapy a small number of observations of the bacteriostatic blood levels attained were made. Various amounts of penicillin were given at fifteen minute intervals for 1¾ or 2¼ hours, the smallest course being eight doses of 12,500 units each (100,000 units in all), and the largest ten doses of 20,000 units each (200,000 units in all). Specimens of blood were taken at intervals by finger prick and the bacteriostatic levels ascertained by Garrod and Heatley's technique.

The results are shown in the table: —

TABLE

Serum No.	Penicillin Total Amount.	In hours	Bacteriostatic levels at hours after treatment commenced 1/2	1	1½	2	3	4	5	6	7
1	160,000	1¾	—	—	—	1/32	1/64	—	1/2	1/2	1/1
2	200,000	2¼	—	1/32	—	1/1,024	—	1/4	1/2	1/1	—
3	100,000	1¾	—	—	—	1/32	1/1	0	—	—	—
4	100,000	1¾	—	1/16	1/8	—	1/1	0	0	—	—
5	160,000	1¾	—	—	—	—	1/256	1/32	1/2	—	—
6	200,000	2¼	—	—	1/2,048	1/256	1/4	1/1	0	—	—
7	200,000	2¼	—	—	1/512	1/256	—	—	—	—	—
8	200,000	2¼	—	—	1/512	—	1/64	—	—	—	—
9	200,000	2¼	—	1/8	—	1/32	1/4	1/4	—	—	—
10	200,000	2¼	1/16	1/16	—	1/32	1/8	—	—	—	—
11	200,000	2¼	1/8	—	1/512	1/16	1/4	1/1	0	0	—

Although the specimens were taken at too irregular intervals to draw any hard and fast conclusions, study of the table shows two points of interest. One is the very marked difference in the blood levels between individuals having the same course of treatment. The other is shown by sera numbers six, seven and eleven and would probably have been found in others if the necessary specimens had been taken. It is that a certain peak is reached after about seven or eight injections and that a fall in titre then occurs in spite of the fact that more penicillin is given. Sera numbers one and two were taken from patients who had a continuous intramuscular drip running

at the same time. This is the reason for the prolonged bacteriostatic level.

In four cases, estimations were carried out on wound exudates simultaneously with the blood examinations.

There was no significant difference between the titres in the blood and in the exudate.

The method of administration employed was to put up a slow saline intravenous drip using the standard army apparatus. The total penicillin required for a course was dissolved in eight ccs. or ten ccs. of sterile saline and drawn up into a ten cc. syringe. The needle of the syringe was inserted into the rubber tubing just above the intravenous needle, and the syringe strapped securely to the forearm and left in situ during the whole period of the course. Every fifteen minutes one cc. of the solution was injected and the drip turned full on for a few seconds to wash the dose rapidly into the vein.

The pH of the saline used was 6.7 and it had previously been tested to make sure that it had no inhibitory effect on the penicillin.

THE LOCAL USE OF PENICILLIN IN WAR WOUNDS OF THE KNEE JOINT

By Major G. Blundell Jones, RAMC, Orthopaedic Specialist.

This paper is presented as an interim report on a method of treatment evolved in the B.L.A. for dealing with wounds of the knee joint with the object of minimising the risk of infection and securing a healed wound in the shortest possible time.

Certain well known cardinal principles of surgery and immobilisation must be observed, and these have been applied so that the patients remain able to be evacuated at any stage without undue risk. This is an important consideration in forward surgery where the prospect of holding is uncertain. To these principles has been added the use of penicillin. The persistence of penicillin injected into the joint has been investigated with a view to obtaining and maintaining adequate concentration over any desired period.

The results of thirty-two cases are too few to justify any definite conclusions, but it is felt that they are encouraging and that the method is worthy of extended trial. If a patient can be given a cool, dry joint with a healed wound in under twenty-one days then his future prognosis should closely approach that of a similar closed lesion of the joint.

THE METHOD

1. *Operation*: The objects of this are:—
   (*a*) Excision of the wound as soon after wounding as conditions allow. The word "excision" is here used in its proper sense, meaning removal of any foreign body and all damaged tissue, including loose bone and cartilage, from the joint.
   (*b*) Closure of the synovial membrane with interrupted sutures. Other layers of the wound are dressed in the usual way with sulphonamide powder and vaseline gauze.
   (*c*) Injection of 100,000 units of sodium penicillin into the joint in five-ten cc. solution, by a needle inserted into the sound side.
2. *Immobilisation*—in a modified Tobruk plaster with strapping extension leaving the knee joint accessible for subsequent inspection and aspiration and the wound for suture. This plaster is slung from a Balkan beam where facilities exist.
3. *Maintenance of penicillin concentration*. The joint is aspirated at intervals of forty-eight hours and the local penicillin replaced by two further injections of 100,000 units. Two aspirations are normally required, the total dosage of local penicillin being then 300,000 units. No pain has been noted as penicillin is injected into the joint.
4. *Closure of Wound*. The wound is sutured in the Tobruk plaster as soon as the appearances of the joint, wound and temperature chart are satisfactory. This is normally five-ten days.
5. *Final Stage*: Nine-ten days after suture, the wound is normally healed and the joint is dry and cool. Sutures are removed and the leg is put in a padded groin to ankle plaster with the

knee-joint five degrees short of full extension, which is sufficient to avoid squeezing inflamed tissues and prevent ligamentous stretching, yet allows easy recovery of full extension on subsequent mobilisation. In this plaster the patient is evacuated to base ready for later mobilisation.

THE USE OF LOCAL PENICILLIN

It is already known that serous membranes present a considerable obstruction to the diffusion of penicillin, and investigations have suggested that the usual dosage (100,000 units daily by continuous intramuscular drip, or doses of 20,000 units 3-hourly by injection) is not likely to produce an adequate bacteriostatic and bactericidal concentration in joints (Rammelkamp and Keefer, 1943).* It may be possible to attain such a concentration by larger dosage, but this would be most wasteful if it can be reached by local application only. Accordingly the latter method was investigated.

The objects of such an investigation must be :—

(*a*) To measure the persistence of penicillin within the joint in order to control the concentration with certainty and if necessary maintain or control the concentration over any given period.

(*b*) To use the information thus gained, in the natural laboratory of the joint, to kill organisms. Here the recent work of Bigger (1944) and Garrod (1945) on bactericidal action must be borne in mind.

One factor is important at this stage, namely—that it is extremely difficult to recover organisms from within a wounded joint at the time it comes to operation ; in the present series of thirty-two cases only one positive culture was obtained. After treatment is begun and penicillin used it becomes even more difficult ; in no case of the present series was a positive culture obtained in subsequent aspirations, although a few degenerate gram positive cocci were seen in the stained film of the centrifuged deposit in five cases.

Bacteriological control has therefore little value and reliance must be placed upon determining the concentration of penicillin, and the application of suitable concentrations in a manner likely to be most effective as judged from experiments in the laboratory. The test of success is the production of an uninfected joint—though here again great caution is necessary in ascribing the result to penicillin when ideal surgical treatment is followed throughout. For this reason no conclusions should be hastily drawn from the present series.

Synovial fluid aspirated from twenty-one knee joints—forty-eight hours after injection of 100,000 units sodium penicillin—was assayed by the "crude cup method" (APLS Current notes) using one drop of undiluted fluid and a control drop of calcium penicillin solution

* Ed. Footnote: Several workers in this theatre (Hughes, Foster and Colquhoun, Simmonds and Jenkins, Lowdon, etc.) have proved that this is not invariably true. Their evidence is printed elsewhere in this brochure. The work recorded in these articles was done in the period August, 1944—March, 1945, and since then further observations made by the same and other officers substantiate the earlier work.

containing 100 units per ml. All assays were carried out against the standard Oxford H. strain of staphylococcus aureus. The figures below refer to the radius of the zone of inhibition in millimetres. Three cases were assayed at twelve hourly intervals, up to ninety-six hours, following a single dose of 100,000 units. Three cases were assayed receiving parenteral dosage as above, and none locally; in none of these cases was a positive result obtained.

21 KNEE JOINTS ASSAYED AT 48 HOURS

Case number	Assay 48 hrs.	Control	Bone injury	Clinical absorption phase
7	10	14	0	0
8	20	20	+	0
16	3	13	0	0
19	3.5	12	+++	0
20	2 (60 hrs)	14	++	0
23	2.5	13	++	0
24	1	11	0	+
25	4 0	13 14	 +	0 +
27	0	13	0	+
28	5	14	+	0
29	6	14	+	0
29 A	0	14	0	+
29 B	8	14	0	+
30	8 0	14	++	0 +
30 A	4	13	0	0
30 B	2.5	13	0	0
31	5 3	 13	 +++	0 +—
31 A	0	13	0	+
32	0 0	 14	 ++	— +
32 A	6	14	0	0
33	4.5 5	13 13	+	0 0

3 *Cases Assayed at Intervals of* **12** *Hours; Single Dose* **100,000** *Units*

Case	HOURS 12	24	36	48	60	72	84	96	Bony Damage
16	+	7	+	3	1.5	5	1	0	0
19	11	6	7	3.5	4	2	0	0	+++
20	+	+	+	+	2	1.5	0	0	0

General considerations suggest that joints with marked bone and cartilage damage would show more rapid absorption of penicillin than those with practically intact synovial membrane. This assumption was not confirmed, early negatives occuring in practically intact joints as well as late positives in severely damaged ones. The only correlation that can be found in this series of twenty-one joints is in the clinical state with regard to the production or absorption of effusion. The occurence of absorption in the table above is denoted by +, and ± the beginning of the phase. It appears almost as though penicillin "goes with the tide". Once the joint is ceasing to produce effusion, or active obvious absorption is taking place, then rapid absorption of penicillin is observed. This is well seen in cases twenty-five, thirty and thirty-one, where two estimations were made at different phases.

It is probable that in a joint undergoing such absorption of effusion the risk of infection is minimal and it may not be of consequence if an occasional negative value is obtained at forty-eight hours.

Moreover, other facts discovered in the laboratory must be taken into consideration if penicillin is to exert its maximum bactericidal effect. (a) If penicillin is only lethal to organisms in a dividing state, a method of application for fractional sterilisation must be employed, (Bigger, 1944). (b) "The bactericidal action of penicillin proceeds at a constant rate regardless of concentration within wide limits if penicillin is used ; impure samples are more effective in low than in high concentrations", (Garrod, 1945). All the penicillin used in this series was impure.

From the practical viewpoint it would appear therefore, that :—

(*a*) Forty-eight hourly aspiration and replacement of penicillin in joints should be continued until more precise information is available. Some of the present noted variations in concentration may be beneficial.

(*b*) After the first period of penicillin protection, to give another dose after an intermission of forty-eight hours, and then again after an intermission of seventy-two hours, *i.e.*, four days and five days after the last previous injections, assuming forty-eight hours penicillin persistence.

(*c*) To investigate the use of a smaller dose (50,000 units) which may well be as effective as the present dose.

ANALYSIS OF THIRTY-TWO CASES TREATED BY THE METHOD OUTLINED

Type of wound	Number	Positive culture at operation	Degenerate gram positive cocci in fluid aspirated
SW (Mortar)	8	1	2
SW (HE)	7	0	2
GSW	8	0	0
BW (Aerial)	2	0	0
BW (Grenade)	2	0	1
Accidents	5	0	0

Wound	Number	Operation after wounding (Average)	No. of Aspirations				Average day of closure	100 percent healing in 10 days
			2	3	4	5		
No bone injury—minor cartilage damage	11	14 hrs	9	2	0	0	7	11
Bone and cartilage injury	21	14 hrs	16	2	2	1	7	18
(a) Bone severe	11		7	2	1	1	7	10
(b) Excision patella	5		3	0	1	1	2 primary 6, 7, 10	5

OPERATION

The average interval after wounding over the whole series was fourteen hours, the longest being sixty hours and the shortest two hours. Three cases of perforating bullet wounds and one of accidental perforation were not opened; the wounds were small with minimal damage shown in X ray, and the operation was confined to aspiration, injection of 100,000 units of penicillin and immobilisation in a modified Tobruk plaster; the subsequent treatment was the same as in the other cases except that suture was not required. It was possible to complete the excision through the original wound, or extensions of it, in twenty-six cases of the remainder, while in the other two a second opening was made and treated exactly as the wound, by synovial suture only and delayed closure.

ASPIRATION

Twenty-five cases required only two aspirations and none more than five. The necessity for aspiration was judged by the following criteria :—

(*a*) The recurrence of effusion.

(*b*) The local temperature of the joint.

(*c*) The appearance of the wound and the temperature chart of the patient.

The maximum local dosage of penicillin was therefore 600,000 units, and the usual dose 300,000 units. No reactions were observed to the use of penicillin within any joint. No parenteral penicillin was used except in three cases with other extensive wounds, and these have been included in the series above. All patients received the standard dose of twenty-five grams oral sulphonamide over five days subsequent to wounding.

CLOSURE OF THE WOUND

It is desirable to minimise scarring and this is achieved by closure of the skin at the earliest safe moment. Nearly all patients were apyrexial in three days but some cases still showed low evening rise. This was disregarded providing the local appearance was satisfactory, the joint was cool, and the effusion was not recurring after aspiration. Suture was confined at this stage to skin only and done in the Tobruk plaster without disturbance. No case was aspirated after suture. The average suture was in seven days, the shortest five days, and the longest sixteen days after the primary operation. There was 100 per cent union in twenty-nine cases of the series in ten days after closure. Sulphonamide powder was the only agent used in the wound.

No case showed any sign of infection of the knee joint on removal of sutures. Three cases showed only partial union of the skin but they too were put into padded groin to ankle plasters for evacuation. The immediate object of the treatment had therefore been achieved in every case. The late results are not yet available but there has been no report of later infection and the few that have come in show function equivalent to similar closed lesions.

SUMMARY

1. A series of thirty-two cases of war injuries of the knee joint is presented in which no case showed infection of the joint and the wounds were completely healed under twenty-one days in twenty-nine cases. Treatment by a standard method suitable for forward surgery is described and penicillin is used locally within the injured joint.
2. The persistence of penicillin used locally in the knee joint has been investigated, from which it appears that 100,000 units dose maintained an adequate concentration for forty-eight

hours unless active absorption of effusion is taking place. Further information is required on the optimum method of employing local penicillin in joints in order to kill organisms in the light of the recent work of Bigger (1944) and Garrod (1945). Parenteral administration in wounds of joints has been abandoned as uncertain and wasteful unless the presence of other wounds requires its use.

I am indebted to Major G. B. Forbes, Pathologist, for the penicillin estimations and bacteriological examinations carried out under field conditions and often at inconvenient hours. My thanks are due to Col. Eccles, O. B. E. for permission to publish the cases, and to Lt. Cols. A. L. Eyre Brook, H. R. Duval, and G. Macpherson for encouragement and helpful criticism.

REFERENCES:

Army Pathological Laboratory Service, Current Notes, X, 52.

Bigger, J. W. (1944), Lancet, II, 497.

Garrod, L. P. (1945), Brit. Med. J., I, 107.

Rammelkamp, C. H., and Keefer, C. S. (1943), J. Clin. Invest., XXII, 425.

ANAEROBIC MYOSITIS IN 21 ARMY GROUP

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The true figures for anaerobic myositis are difficult to obtain. If we accept the official reports on gas gangrene (A. Fs. I. 1241) as our guide we get the following figures for the period June, 1944 to February, 1945.

TABLE I

Total Anaerobic Myositis Cases for nine months (A. Fs. I. 1241)

Categories	Total cases	Deaths	Percentage Recovery
Allied troops	115	20	82.6
Prisoners	41	12	70.7
TOTALS	156	32	79.5

On the other hand if we accept the various surgical and other reports submitted to the Consulting Surgeon as the basis for calculation, and get the information checked by direct investigation on the spot, the following figures are obtained.

TABLE II

Total Anaerobic Myositis Cases for nine Months (Corrected Figures)

Categories	Total cases	Deaths	Percentage Recovery
Allied troops	238	52	78.1
Prisoners	118	57	51.7
TOTALS	356	109	69.4

There is a serious discrepancy between the two tables, and much as we should like to believe No. I, we know that No. II is much more accurate for the following reasons :—

1. The majority of the A. Fs. I. 1241 were rendered by hospitals, and a minority by forward surgeons although they have in fact treated more cases of gas gangrene. A number of these surgeons have never heard of A. F. I. 1241 or find it convenient to forget it.
2. It was discovered that certain surgeons genuinely believed the form had not to be rendered in P.W. cases.

3. Major J. D. MacLennan, O. C. No. 7 Mob. Bact. Lab., who was continuing his studies on gas gangrene, spent most of the time under review in this theatre. He investigated not only those cases reported on the official forms, but *also* others discovered by us during routine tours or from the study of surgical and death reports, etc. After personal investigation, Major MacLennan gave us corrected figures to the end of January, 1945, and stated that in his opinion, with the possible exception of about twenty cases, they were all genuine. We can confirm from our own observations that the diagnosis of gas gangrene was occasionally made on inadequate grounds by the less experinced surgeons.

Table II consists of the figures corrected to 31 January 1945, by Major MacLennan, with the February figures added to them. Table I is completely inaccurate, and reveals how misleading results may be produced by anyone who relies entirely on records unsupported by personal investigations. On the other hand the records probably provide a "fair sample" of the cases, although they are useless for computing the true incidence and mortality.

As will be shown later, in this campaign the incidence of anaerobic myositis in Allied troops has been low, and the recovery rate more favourable than usual. It would be very interesting to discover why, but this is far from easy. The surgical and death reports merely provide summaries and contain insufficient information for detailed analysis, while even in the more elaborate records on A. Fs. I. 1241 there are many omissions and ambiguities. These are often not due to carelessness. It is sometimes impossible to obtain the required particulars. Many patients, for example, are very hazy about dates and times of wounding, essential details (chemotherapy, surgery, dates, dosages, etc.) may not be recorded on the field medical card and cannot be obtained from any other source, and a proportion of both Allied and enemy wounded speak no language understandable by the medical officers concerned. It is not surprising, therefore, that in 156 records there were only seventy-eight sufficiently complete to justify a detailed analysis, and even then it was impossible to obtain information about every point.

Amongst the seventy-eight records analysed fifty-nine referred to Allied troops with eight deaths, and nineteen to German cases with four deaths. No definite conclusions can be based on such small groups. Nevertheless certain suggestive evidence can be extracted as to why the incidence and mortality in prisoners is higher.

TIME INTERVALS

There is general agreement that the time interval between wounding and primary surgery is highly important. It was determined in forty-eight cases.

In thirty-five Allied cases this interval averaged 17.2 hours.

In ten Enemy cases it averaged 26.1 hours.

In three Allied paratroopers it averaged 52 hours. Paratroops cannot always get treatment as early as ground troops, and in Tables III and IV they are recorded separately. Any comparisons made now or later refer to the other groups. On this basis it will be seen that the Allied cases received primary surgery on an average about nine hours earlier than prisoners. Amongst the total 48 cases, in eighteen the interval exceeded twenty hours.

PRIMARY SURGERY

There is equal agreement that adequate primary surgery is of vital importance in preventing or eliminating infection. The following table provides information on this point. Cases recorded in column one apparently had adequate primary surgery, while those in column three had none. The second column contains thirteen cases where the records are indefinite on this point, and also five cases where there is a remark that excision or relief of tension had been inadequate at the first operation.

PRIMARY SURGERY

TABLE III

Categories	Adequate Primary surgery	Inadequate or doubtful primary surgery	No primary surgery	Total cases
Allied troops	35	12	5	52
Prisoners	10	5	4	19
Allied Paratroops	3	1	3	7

This table shows that sixty-seven per cent of the Allied troops and forty per cent of the prisoner cases had adequate primary surgery.

SURGERY FOLLOWING DIAGNOSIS

It is impossible to assess the quality of this from records, but as far as can be determined it was prompt and efficient. In at least fifteen cases the infection was established before admission to a surgical unit, and three of these men died—one without operation, and two who were operated upon at some unknown interval after the onset.

There were forty-three primary amputations in the series, and two secondary amputations following traumatic amputations by a missile. The rest were treated by excision. By reference to Table VII it will be seen that thirty-eight amputations were performed in men with major vascular injuries, and a number of these would have required amputation in any case.

PROPHYLACTIC DRUGS AND SERUM

While opinions vary about the exact value of these, most surgeons believe that they help in preventing or controlling infection.

ADMINISTRATION OF PROPHYLACTIC AGENTS

TABLE IV

Categories	Total cases	Penicillin			A. G. G. S.			Sulphonamides		
		Given	None	Doubtful	Given	None	Doubtful	Given	None	Doubtful
Allied troops	59	32	24	3	31	27	1	31	26	2
Prisoners	19	1	18	—	5	13	1	12	6	1

This table shows that 53–54 per cent of the Allied cases had received prophylactic penicillin, A. G. G. S. and sulphonamides. Percentages may be misleading in small groups so they are not given for P. W. cases, but it will be evident that a much smaller proportion received penicillin and A. G. G. S. and a higher proportion received sulphonamides. Naturally while penicillin was in such short supply prophylactic sulphonamide was used in preference to penicillin in prisoners, unless there was some special reason for giving penicillin. Normally in our armies sulphonamides are used as a routine for prophylaxis, but about half our forward units were deliberately not using it *if* penicillin was being administered.

Unless all other relevant factors are considered erroneous deductions may be made from this table. Thus knowing that the incidence of myositis is higher amongst prisoners it might be asumed that penicillin is a better prophylactic agent than sulphonamide. Or it might be argued neither was any good, unless one remembered that in many cases with vascular injuries the agent probably never reached the affected part in adequate concentration. And there are other factors such as time intervals, primary surgery, state of nutrition, etc., to be considered. The solution of any problem with many variables is never easy.

ADMINISTRATION OF THERAPEUTIC AGENTS

TABLE V

Categories	Total cases	Penicillin			A. G. G. S.			Sulphonamides		
		Given	None	Doubtful	Given	None	Doubtful	Given	None	Doubtful
Allied troops	59	53	—	6	49	2	8	37	8	14
Prisoners	19	10	7	2	17	2	—	16	1	2

This table gives an idea of the use of penicillin, A. G. G. S. and sulphonamides after the diagnosis of anaerobic myositis was made. The first column shows those who apparently received adequate doses, the second those who received none, and in the third are shown those cases where the dosages were inadequate or where the records are too indefinite to be certain of the facts. Thus any patients receiving less than 150,000 units parenteral penicillin, 50,000 units A. G. G. S. and 12 grams sulphonamide are included in column three, as are also those men who only had local applications of penicillin or sulphonamide. Possibly these limits are set too low, but in fact if

the agents were given at all they were usually given in adequate or even excessive dosages. Thus one man had 2,100,000 units penicillin and another had 437,500 units A. G. G. S. The maximum oral dosage of sulphonamide noted was forty-five grammes sulphathiazole.

It will be seen that a higher proportion of Allied troops than prisoners received penicillin, and in the case of sulphonamides the position is reversed.

The next table shows the chemotherapy and serotherapy given to the men who died.

CHEMOTHERAPY AND SEROTHERAPY IN FATAL CASES

TABLE VI

Administration	Penicillin	A. G. G. S.	Sulphonamides
No prophylactic; adequate therapeutic	4	8	4
Adequate prophylactic and therapeutic	3	2	6
None at all; or inadequate doses	5	2	2
TOTALS	12	12	12

The only conclusion one can draw from this table is the fact that drugs and sera, even in adequate dosages, will not save every case. It should be stated that one of the twelve deaths in this series was due to an associated abdominal wound, another man died on the table, one was moribund before he reached a surgeon, three were fulminating cases, and four had high arm or thigh amputations. Considered from another aspect, four had gas gangrene localised to one muscle group, five had more than one group invaded, and three were fulminating cases showing rapid and widespread invasion.

ONSET

The infection must be present for some time before it is detected, but naturally the only ascertainable figures refer to the time when the disease was first noted clinically. In sixty-two cases where this point can be determined the onset was noted 2.4 days after wounding. The extremes were one day and seven days, if one misses out the two following cases. In one the onset was said to be $2\frac{3}{4}$ hours after wounding; this case would have been excluded altogether were it not for the fact that sections of the muscle were reputed to show changes typical of anaerobic myositis ; the patient did well following excision of the affected area. The other man developed gas gangrene twelve days after wounding ; the wound was sutured five days after wounding, and the first signs of myositis were detected seven days later; he too did well following excision of

the muscle. The condition was established before admission in at least fifteen cases.

TYPES OF WOUNDS

In thirty-one cases the degree of muscle damage was regarded as slight to moderate, and in forty-seven it was said to be very extensive.

The reputed causes were as follows :—

Shell wounds	39
Gun-shot wounds	12
Mortar-bomb wounds	11
Mine wounds	7
Missile uncertain	6
Accidental injuries	3

There were associated fractures in thirty-five cases.

THE PARTS AFFECTED

The following were the sites of the anaerobic myositis. There were five generalised and three fulminating cases in the series, and in these the site of origin was selected in compiling the following figures.

Leg	45
Thigh	18
Arm	6
Buttock	4
Shoulder	2
Foot	2
Back	1

The high incidence in the lower limb is noteworthy, and should be considered in conjunction with Table VII. The leg is much the most common site, and it is interesting to note that of the forty-five cases thirty involved the posterior groups, twelve the anterior group, and three were generalised and involved muscles in both. The posterior tibial artery was also more frequently damaged than any other, and there is another possible factor concerned. There are two layers of fascia in the calf, and tension in the deeper compartment is not relieved by incision of the superficial fascia alone.

PREDISPOSING CAUSES

Certain figures relating to predisposing causes such as lengthy time intervals, the absence of primary surgery, inadequate chemotherapy, and extensive muscle damage have already been given.

In five cases a tourniquet had been applied and in another patient one had probably been used. In one case the tourniquet had been in position ten hours. In two cases it was noted that tension had not been prevented or relieved by splitting the deep fascia at the primary operation, and in two others the patients arrived with tight, unsplit plasters.

Associated vascular injuries are undoubted predisposing factors, and their incidence is shown in the following table: the final column shows the number of cases requiring amputation.

ASSOCIATED VASCULAR INJURIES

TABLE VII

Vessel Involved	Definite injury	Probable injury	Amputation
Post. Tibial Artery	15	2	12
Popliteal Artery	7	1	8
Ant. Tibial Artery	6	—	4
Femoral Artery	5	—	4
Both Tibial Arteries	4	1	5
Brachial Artery	2	—	2
Superior Gluteal Artery	2	—	—
Plantar Arteries	1	—	1
Axillary Vein	1	—	1
Popliteal Vein	1	—	1
TOTALS	44	4	38

FOREIGN MATERIAL

Curiously enough the official form asks for no information on this point, and it is impossible to discover how many wounds contained pieces of cloth, metal or other foreign material or whether they were obviously contaminated with soil or mud.

BACTERIOLOGY

The information on this point is very incomplete. In thirty-three cases Cl. welchii was definitely identified. In three cases this organism was associated with Cl. sporogenes, in one with Cl. tetani, and one wound contained Cl. welchii, Cl. sporogenes, Cl. bifermentans, and Cl. tertium. Many had concomitant infections with aerobic organisms. Cl. oedematiens was only found in one case in this series.

In twenty other cases clostridia were identified, but the exact types are not specified.

In twenty-four there is no information about the bacteriology, but clinically there was no doubt about the diagnosis.

An interesting observation was made by Major J. D. MacLennan. He obtained smears from a number of severe and contaminated wounds before primary surgery had been performed and isolated Cl. welchii in about eighty per cent. In similar wounds investigated by the same observer in the desert Cl. welchii were found in twenty-eight–thirty per cent of cases.

DISCUSSION

The figures supplied support the common view that anaerobic myositis is more liable to develop in severe wounds. In this series a high proportion were severe as is shown by the fact that about fifty per cent had very extensive muscle damage, about forty-five per cent had associated fractures, and, probably most significant of all, about sixty per cent had associated vascular injuries. Any severe injury devitalises the tissues, and if a vessel is also injured the condition is aggravated. The supply of oxygen is cut off, metabolites are not removed, the normal defence mechanisms are lacking, prophylactic agents given orally or parenterally cannot reach the affected parts, the damaged tissues may die, and the area becomes an increasingly favourable site for unchecked bacterial proliferation. Of course the association is not invariable, and in the nine months under review at least 900 men in this theatre had severe wounds complicated by main vessel injuries, and the great majority did not develop gas gangrene. The blood supply may be interfered with in other ways and in this series tourniquets, tension due to undivided fascia, and unsplit plasters were all implicated on occasion.

INCIDENCE AND MORTALITY RATES.

The incidence was much higher amongst prisoners, and although we can give no figures in support, our impression is that during the period under review the proportion of severe wounds was higher amongst enemy wounded than amongst our own troops, and that their states of nutrition and bodily cleanliness were on a lower level. A retreating army may secure its lightly wounded, but may be forced to leave the more serious and helpless cases behind. This is one possible reason for the higher incidence amongst prisoners. And there are others. The average time interval between wounding and primary operation was definitely greater amongst prisoners, and a higher percentage had no or inadequate primary surgery. These factors alone are sufficient to explain a disproportionate incidence, and largely invalidate any attempts to evaluate other factors such as chemotherapy. Nevertheless it should be noted that Allied troops received much more prophylactic penicillin and that prisoners received more prophylactic sulphonamides. In regard to the therapeutic use of these drugs the same thing occurred, but the disparity was less pronounced.

We can give no information about the value or otherwise of antitoxins either in prophylaxis or therapy. Others much more competent to do so will doubtless review this problem.

The incidence and mortality amongst Allied troops is a different problem. Here factors such as time intervals, primary surgery, nutrition, etc., are less variable yet the incidence and mortality rates are more favourable than usual in this serious infection. According to MacLennan the incidence was 3.4 per 1,000 in the Middle

East and 6.7 per 1,000 in Tunisia; and Jeffrey and Scott Thomson estimated the figure in Italy would be not less than 10 per 1,000.

It is uncertain on what basis these incidence figures were calculated—whether on the total casualties in the respective campaigns or on "split" figures supplied by a statistical department. It is difficult to arrive at a true figure, because obviously a proportion of the men injured by enemy or non-enemy action have lesions that are most unlikely to lead to the complication of gas gangrene; we have discovered that this proportion cannot be determined with accuracy from any available source. Our calculations are based on "split" figures kindly supplied by Q (AE) Stats., 21 Army Group and the figures include all men injured by enemy or non-enemy action who were treated in medical units in 21 Army Group during the period November, 1944 to April, 1945. The statistical branch state that the figures for Allied troops are accurate within narrow limits, but for prisoners they are less accurate. When they are correlated with the anaerobic myositis cases occurring in the same period we find that the incid nce in Allied troops was 1.5 per 1,000, and in prisoners between twenty—thirty per 1,000 cases treated in British units.

Unfortunately no detailed figures suitable for "splitting" were available prior to the end of October, 1944, and the above quoted incidence figures are, therefore, not accurate for the whole campaign from D day to V. E. day. It is believed that in the earlier months the incidence in Allied troops was almost double, i.e., about three per 1,000; but Major J.D. MacLennan informed us verbally before he left this theatre in February, 1945, that the incidence of gas gangrene had been lower here than in any other campaign.

"The case fatality rate of gas gangrene in the present war has been approximately fifty per cent". (MacLennan and MacFarlane, 1944). The rates have fluctuated at various times and places from approximately seventy per cent in Sicily in 1943, to thirty per cent in Italy in December 1943. However, in the previous three months in Italy the mortality rate was seventy per cent. In a series of thirty-three cases occurring in Italy in the Spring of 1944 the mortality was 36.4 per cent (Jeffrey and Scott Thomson). Here in 238 Allied cases treated by many different surgeons the mortality rate has been 21.9 per cent.

Factors influencing the occurrence of infection and the results have already been discussed by us in another section, so we shall only repeat that the one new factor in this theatre has been the widespread use of *both* parenteral and local penicillin at the most forward surgical levels. We cannot escape the conclusion that this potent agent must be accorded a good deal of the credit for the diminished incidence and improved results.

REFERENCES

Jeffrey, J. S. and Thomson, Scott (1944), Brit. J. Surg., XXXII, 159.
MacLennan, J. D. (1944), Lancet, I, 203.
— and MacFarlane, M. G. (1944), Brit. Med. J., I, 683.

PENICILLIN IN CHEST INJURIES

By Major J. Leigh Collis, RAMC, O.C. No. 3 Surgical Team for Chest Surgery, Capt. J. H. Marshall, RAMC, Physician, and Capt. P. Stuart Smith, RAMC.
With Bacteriological Appendix by Major K. E. A. Hughes, RAMC, O.C. No. 3 Mob. Bact. Lab. and Major T. Simpson, RAMC, Specialist Physician.

PART I

From No. 3 Surgical Team for Chest Surgery.

Reference to any of the recent papers on the place of penicillin in the treatment of chest injuries shows that this problem is by no means settled. The experience of some 948 admissions to No. 3 Surgical Team for Chest Surgery is presented here in the hope that it will serve to make the position a little clearer. Only the details relevant to penicillin treatment are considered, so that this report is in no way a comprehensive study of general practice.

Haemothorax — This group includes only cases with definite clinical and radiological evidence of fluid. It does not include patients with traces of blood, where aspiration was not necessary, or where only a specimen was obtained. Further patients with a haemopneumothorax or a haemothorax associated with a sucking wound are treated separately. Table I records some details regarding 138 examples of this condition from which six instances have been excluded because they were received by the Team as empyemata ready for drainage. It is emphasised that only such far advanced cases of infection are excluded, while any case in which there was the slightest hope of avoiding drainage is retained in the series. This means that several patients in the series were admitted with infected haemothoraces which might even be offensive or showing early purulent change. The size of the haemothorax is given as either small, medium or large. The small ones are those which produced under ten ozs. of fluid at any one of their early aspirations. The medium group yielded ten to twenty ozs. while the large group produced more than a pint. The presence of a bronchial fistula is recorded, if this was present in the early stages of treatment, and therefore a case in which it was present only after the onset of established infection would not be mentioned as such.

TABLE I

	Gross Total	No. Cases excluded	Net Total	Size of Haemothorax			Deaths	Bronchial Fistula	Evac. with fluid	Clot	Required Drain.	Allied	Penicillin given	Drain and Pen.	Drain. No. Pen.
				S	M	L									
Non-sucking Haemothorax	138	6	132	45	27	60	3	0	15	13	9	104	94	7	2
											6.8 %			7.4 %	5.3 %
Empyemata of above series	15	6	9	1	2	6	1	0	—	3	9	6	7		

Many of the patients treated by this Team were evacuated before it was possible to be certain of their final outcome. For this reason, a column showing "evacuated with fluid" has been given. It will be seen that this was not a very large group, and information obtained from follow-up cards does not suggest that any considerable allowance is necessary on this account. Figures for the incidence of clot are bound to be rather inaccurate. It is clear, from experience of early thoracotomies, that there always is some clot in any haemothorax so that, when a case is recorded as having clot, it means that this was a point of clinical concern in the treatment of the case. Assessment is less likely to be difficult in the group of cases producing clotting of later occurrence from fibrin secondarily introduced with effusion fluid.

Some difficulty was experienced in deciding at what point in the development of sepsis a patient was considered to have crossed the line. Isolated positive cultures are common and could probably be found in every case if investigation was sufficiently carefully carried out. We have taken the dividing line as the time when it became obvious that drainage was required. Once patients have reached this point, we have had no success from any treatment with or without penicillin which was short of drainage, so that, particularly in our hands, this point marks a very clear cut division. It does not necessarily mean that all these cases were drained while with the Team. Some were sent to the United Kingdom for drainage, while two cases which were not actually under this group were fatal from various reasons before drainage was instituted.

It will be seen that intrapleural penicillin was widely used, but that there were thirty-eight patients who did not receive it. This latter group has allowed a control series, as shown in the last two columns. The empyema rate of 7.4 per cent with intrapleural penicillin compares favourably with other published and comparable figures, which show percentages of thirty or over, but the most

extraordinary thing is that the results without penicillin are as good. Actually, they are slightly better, but the small series only allows of the assumption that there was no great difference. There is one factor which weighed against the penicillin group and this was that some patients, who would not otherwise have had penicillin, were given it because of early infection. Throughout the greater part of our work, such action has been rigidly avoided and it is not considered to be a big factor in the interpretation of results.

A second line of figures in Table I gives some further details about the nine cases requiring drainage. It will be seen that relatively more of these patients had had large haemothoraces and intrapleural clot.

The dosage of penicillin which has been used intrapleurally has been 50,000 units in two c.c. of water every two days. This appears to be adequate, while further increase does not appear to prolong the time for which penicillin is effective. This side of our treatment is being dealt with in a report by Major K.E.A. Hughes, based on investigations carried out when he was working in conjunction with this team. In view of this, the figures concerning dosage of penicillin, its persistence, and the bacteriological findings, are not repeated here. The only point in our treatment at variance with other writers is the small quantity of fluid in which we dissolve the penicillin. We have always considered that complete aspiration was of first importance and that nothing should be allowed to interfere with this. On this account, the introduction of fifty c.c. fluid was against our principles, and undoubtedly gave rise to the possibility of introducing air. This practice has been amply supported by our experience, as we have not found any material increase in the incidence of clotting, and, further, the injection is not painful. Pain has been present on three occasions after injection, but, in each case, the cause was obvious. Twice, it was injected into the diaphragm, giving pain in the shoulder, and once into the intercostal muscle. It might also be mentioned here that we have not found any empyema produced by organisms introduced with the penicillin.

Haemopneumothorax. — Eighty-four instances of this condition were treated and are reviewed in a similar way to haemothorax. It will be seen that six cases are excluded on similar grounds, as they were admitted requiring immediate drainage. Of the remaining seventy-eight, there were eight patients that required drainage. This gives a 10.3 per cent incidence which will be seen to be greater than with simple haemothorax. This finding would be expected, since, among other things the extent of the trauma is greater in this group. In view of this, it was rather anticipated that this series would be more likely than the preceeding one to demonstrate the benefits of penicillin. However, the control series shows the remarkably low incidence of six per cent. Here again, the control series is small, but the findings are consistent with Table I, and may at least be taken as showing no great improvement from the use of penicillin.

TABLE II

	Gross total	No. cases excluded	Net Total	Size of Haemothorax S	M	L	Deaths	Bronchial Fistula	Evac. with Fluid	Clot	Required Drain.	Allied	Penicillin given	Drain and Pen.	Drain. No Pen.
Non-sucking Haemopneumothorax	84	6	78	18	16	44	1	24	11	10	8 10.3 %	55	45	6 13.3 %	2 6 %
Empyemata of above series	14	6	8	2	1	5	1	4	—	2	8	6	6		

Sucking wounds with haemothorax. — This group, the details of which are set out in Table III, includes all sucking wounds with sufficient blood in the pleura to require aspiration, while, of necessity, these patients had air also in the pleura at some time in their course. The number of cases excluded, which is rather high, was due, in considerable measure, to prisoners of war evacuated from German hospitals after indifferent early treatment. Again only those cases

TABLE III

	Gross total	No. cases excluded	Net Total	Size of Haemothorax S	M	L	Deaths	Bronchial Fistula	Evac. with Fluid	Clot	Required Drain	Allied	Penicillin given	Drain and Pen.	Drain. No Pen.
Sucking wounds Haemothorax	206	25	181	46	62	73	6	28	50	33	21 11.6 %	153	149	16 10.7 %	5 15.6 %
Empyemata of above series	46	25	21	3	8	10	3	11	—	4	21	15	16	—	—
Sucking wounds No Haemothorax	40	—	40	—	—	—	0	—	—	—	1 2.5 %	34	0	—	—
Sucking wounds excluded	12		12	Cause of exclusion—early evacuation and unsatisfactory record of progress. There were no cases of pleural infection in this group.											
Total number sucking wounds excluded	245	—	220	—	—	—	—	—	—	—	21 9.5 %	—	—	—	—

are excluded who were admitted in such an advanced state that drainage was at once indicated, or had already been performed. In general, the figures are reached in exactly the same way as in the preceeding groups. The twenty-one patients who required drainage gave an incidence of 11.6 per cent, which will be seen to show a steadily increasing danger through the three tables now given. This is in conformity with the degree of tissue trauma that might be expected in these cases. In this group the control series shows an advantage from the use of penicillin. The empyema incidence without penicillin being 15 per cent against 10.7 per cent with the drug.

Sucking wounds without haemothorax. — Also included in Table III is our experience with sucking wounds who had no haemothorax after initial surgical treatment. Of these forty patients, there was only one instance of infection that required drainage. The circumstances in this single case were rather exceptional as his pleura was already obliterated, so that satisfactory suture of his badly lacerated lung was impossible. This, together with the heavily infected and late nature of the wound when it arrived at operation, resulted in the development of a lung abscess. The fact that this group was not complicated by haemothoraces implies that in many of them the wounds were not severe, but this was not always the case.

The extremely low infection rate in this special group of sucking wounds must be considered in conjunction with the rising empyema incidence through the series of haemothorax, haemopneumothorax, and sucking wounds with haemothorax. Comment has already been made that this rising infection rate is probably associatedwith a greater degree of trauma to either the chest wall or the lung. There seems little doubt that this is a true finding, but the rise is a comparatively small one, and hence the infecting factors outside the pleura should not be over-emphasised. It is this point that the experience with the sucking wounds without haemothorax demonstrates well. It shows that, providing the surgery is adequate, the danger of a pyothorax is minimal as long as the pleura is dry.

Chest wall wounds. — It is not felt that there is a necessity for expansion on this subject, as it will be covered by the general papers on wound infection. However, a few words must be said to make clear the figures shown in the tables with reference to our treatment of these wounds. Except for a small group of cases treated recently, it has not been our practice to use intramuscular penicillin, save in isolated cases, so that our figures can be taken as representing intrapleural penicillin therapy only. The treatment of the wound has been associated with local sulphonamide, while the skin has been left open for secondary suture in five days.

Satisfactory results have been reported (d'Abreu, A. L., Litchfield, J. W. (1945), B. M. J., I, 553) from the use of penicillin introduced

through wound tubes in the treatment of infected sucking wounds. We have not employed this method, but have had satisfactory results from a different line of treatment. In this, secondary suture follows pleural and wound lavage, while special attention is given to making the wound secure from within by producing pulmonary re-expansion (Collis, J. L., Davison, M. H. A., Smith, P. S., Lancet, awaiting publication).

Total admissions. — Table IV has been included partly because there are causes for empyema not already given and partly because other writers have used this as a basis for the calculation of empyema rate. These 948 patients, from whom forty-eight have been excluded for reasons as already given, represent a very wide variety of conditions affecting the chest. Some were found to have only chest wall involvement, and others had intrathoracic injury without pleural penetration. The forty-two empyemata which occurred will be seen to be an increase of three on the total already given. Two of these cases followed post-traumatic pneumonia, and one was secondary to a subphrenic abscess.

TABLE IV

	Gross total	No. cases excluded	Net total	Required drain.	
Total admissions to 3, S. T. C. S.	948	48	900	42 4.7%	2 pneumonia following trauma. 1 following subphrenic from penet. abdomen

CONCLUSIONS.

The figures that are presented demonstrate that the routine use of intrapleural penicillin is unnecessary. Although this may seem a surprising conclusion, consideration of the conditions makes it easily understandable. In view of the fact that the danger of infection in sucking wounds without haemothorax is negligible, it is clear that, providing haemothoraces are efficiently aspirated, the same results should be obtainable unless clot is present. Further, if clot be present, the organisms will be protected from the injected penicillin, so that, in either circumstance, little benefit can be expected.

In contradistinction to the routine use of intrapleural penicillin, there do appear to be indications for its use in selected cases. First, in cases of early infected haemothorax, it does seem to be of real value. Although the figures have failed to demonstrate it, we do still consider that complete subsidence of the condition may be effected in some cases only with the help of penicillin. An even greater benefit derived from its use in these cases is obtained from the delaying action that penicillin exerts on the formation of an empyema. This allows of a total pyothorax being converted into a localised empyema

before drainage is necessary. In order to demonstrate this point by figures, it would be necessary to have the total periods of treatment and final results of a large group of cases and this we are unable to provide. Secondly, intrapleural penicillin should be valuable for similar reasons where delayed operative intervention is required for foreign bodies or clotted haemothoraces. Thirdly, when the stress of circumstances is so great that adequate aspiration and other treatment is impossible, there may be reason for the use of intrapleural penicillin. Fourthly, where there is extensive tissue damage, as in many sucking wounds, intrapleural penicillin would seem to be an advantage, as is demonstrated by the figures in Table III.

Above all other conclusions we feel our figures demonstrate well that good general treatment is of first importance. This is borne out by the steadily decreasing infection rates that all recent papers have produced and exemplified by our 7.7 per cent rate for drainage of empyemata in the total 491 haemothoraces of all types. The importance of good general treatment is further emphasised by the drainage rate with and without penicillin. In 388 haemothoraces of all types with penicillin the rate was 7.5 per cent against 8.7 per cent for 103 cases treated without penicillin.

SUMMARY

1. Penicillin is not required intrapleurally as a routine in the treatment of haemothorax.
2. There are four special groups of patients in which its intrapleural use is required:—
   (a) Early infected haemothorax.
   (*b*) After surgical treatment of sucking wounds complicated by haemothorax.
   (*c*) In association with delayed operative procedures involving the pleura.
   (*d*) In haemothoraces, if circumstanses prevent adequate treatment.
3. Intramuscular penicillin should be used to aid early wound healing and in the treatment of any case with extensive tissue damage.

BACTERIOLOGICAL APPENDIX ON PENICILLIN IN CHEST INJURIES

PART II

From No. 3. Mobile Bacteriological Laboratory.

In conjunction with No. 3 Surgical Team for Chest Surgery an investigation was carried out on the effect of intrapleural penicillin on the bacteriology of thoracic wounds.

It was commenced in August 1944, but unfortunately owing to military necessity it was prematurely terminated. Also at that time evacuation of cases from hospital was rapid and it was not possible to follow up the cases as long as was wished.

In all, sixty-nine cases were investigated but only thirty-four of these could be retained under observation for four or more days.

METHODS EMPLOYED

Specimens of the pleural contents aspirated by Major T. Simpson were put into sterile, screw-capped, glass bottles containing sufficient sodium citrate to prevent clotting and were stored in a refrigerator until they could be examined. This period never exceeded ten hours.

Smears and aerobic cultures were made from all specimens, and anaerobic cultures in Robertson's Meat medium from those in which the smears suggested the presence of clostridia. No attempt was made to differentiate between the species of clostridia, and penicillin sensitivity tests were not carried out on them, but all aerobes had their sensitivity investigated by the filter paper method using the standard staphylococcus for comparison.

At the time no penicillinase was available for incorporation in the medium, but an attempt was made to dilute out any penicillin present in the specimens by spreading a loopful of the material over as large a surface of medium as possible. This was successful, as sensitive organisms were frequently grown from specimens containing considerable amounts of penicillin. The presence or absence of penicillin in the fluids was demonstrated by the assay cylinder method, the specimens having first been centrifuged or the more solid contents having been allowed to separate out by gravitation. The dosage of penicillin employed was 50,000 units of the sodium salt (Pfizer) dissolved in 5 c.cs. of sterile distilled water. Although during the period of this investigation 5 c.cs. were used, our general practice is to use 2 c.cs. This was injected into the pleural cavity on each occasion on which an aspiration was carried out, usually every forty-eight hours. No intramuscular penicillin was given while in the hospital.

The types of wounds investigated fall into several classes :—

1. Haemopneumothorax sucking (H.P.S.)
2. Haemopneumothorax closed (H.P.)
3. Haemothorax (H.T.)
4. Any of the above with a retained foreign body (F.B.)
5. Thoraco-abdominal wounds (T.A.)

The letters in brackets are used in the tables to indicate the type of wound together with the following abbreviations :—

I.P. = Intrapleural injection.
I.M. = Intramuscular injection.
P + = Penicillin sensitive.
P — = Penicillin insensitive.
P ? = Sensitivity not tested.

In assessing infections of the pleura, staphylococci which were coagulase negative were not considered as being potentially pathogenic, and no reference is made to them. If they were the only organisms present the pleural fluid was classified as not infected. Among the sixty-nine cases, eighteen were infected when first examined. Table I analyses these showing the type of wound,

TABLE I

Case No.	Wound	Days since wounding	Organisms present	Previous penicillin units
2	H.P.S.	16	Clostridia P ?	150,000 I.P.
3	H.T.	18	Clostridia P ?	400,000 I.P. 750,000 I-M.
13	H.P.S.	3	Clostridia P ?	0
15	H.T.	5	Strep. haemo. P +	100,000 I.P.
16	H.P.	6	Coliform P — Clostridia P ?	100,000 I.P.
26	H.P.S.	5	Strep. haemo. P +	0
27	H.T.	3	Staphylococci P +	0
35	T.A.	13	Proteus P —	0
38	H.P.S.	11	Proteus P — Clostridia P ?	200,000 I.P.
41	H.T.	2	Staphylococci P +	0
52	H.T.	9	Haemophilus P —	?
54	T.A.	16	Strep. haemo. P +	150,000 I.M.
55	H.T.	14	Coliform P —	300,000 I.P.
58	H.T.	13	Strep. haemo. P +	0
63	H.T.F.B.	18	Strep. anhaemo.P?	0
66	H.T.	6	Staphylococci P +	0
68	H.T.	9	Coliform P —	60,000 I.P.
69	H.T.	6	Strep. viridans P —	0

infecting organism, interval since wounding and the amount of penicillin given before the cases came under observation. The penicillin dosage is probably not always correct, owing to the difficulties in documentation at that time.

SUMMARY OF TABLE I

Wounds		*Infecting organisms found*	
		Clostridia	5 times
		Strep. haemolyticus .	4 times
Haemopneumothorax sucking .	4	Strep. viridans . .	1
,, not sucking .	2	Strep. anhaemolyticus	1
Haemothorax	9	Staphylococci . .	3 times
Haemothorax with foreign body	1	Coliform . . .	3 times
Thoraco-abdominal . .	2	Proteus . . .	2
		Haemophilus . .	1
	18		20

Two cases had double infections.

Although clostridia were found on five occasions there was no clinical evidence of gas gangrene. The variety of organisms found is also of some interest. Staphylococci do not predominate as is usual in flesh wounds — in one series of eighty-two simple flesh wounds this organism was isolated from thirty-two on the first examination.

Of the fifty-one cases which were sterile when first seen, only twenty-five could be kept under observation for four or more days. Eighteen of these remained sterile during periods of observation of 4–19 days, the quantities of intrapleural penicillin they received varying between 150,000 units and 500,000 units, or three to ten injections of 50,000 units each. Six had had 100,000 units or less intrapleurally before admission and one had had 450,000 units by the intramuscular route.

The subsequent history of the seven cases in which organisms remained in the haemothoraces in spite of penicillin are as follows :—

CASE 14 — H.T.S. was found to be infected with an insensitive staphylococcus at the time of the second aspiration and after having had one injection only of 50,000 units. As the organism was insensitive no further penicillin was given, but on aspiration eight days later the fluid was found to be sterile. This emphasises the difficulty of assessing the importance of isolated positive cultures, and demonstrates that penicillin must not always be given the credit for preventing the development of an established empyema.

CASE 42 — H.T. After eleven days observation and 250,000 units of penicillin an insensitive staphylococcus made its appearance. Penicillin was continued and on the 16th day after 400,000 units of penicillin a sensitive haemolytic streptococcus was grown. In spite of retaining its sensitivity this organism was found on each subsequent examination until the patient was evacuated on the 31st day. A total dosage of 700,000 units had failed to eradicate it.

CASE 44 — H.P.S. Was found to be infected with a coliform bacillus on the 11th day of observation and after 350,000 units. Only one more injection was given and he was still infected when evacuated on the 29th day.

CASE 48 — T.A. After 200,000 units and on the 3rd day of observation a coliform bacillus was found. One further injection was given. Coliform bacilli disappeared spontaneously eight days later. After a further fifteen days, during which time no penicillin was given, an insensitive staphylococcus appeared and was still persisting when he was evacuated on the 27th day. Here again even B. Coli is found disappearing by aspiration treatment alone.

CASE 50 — H.T. This case was found to be infected with a coliform bacillus on the 6th day of treatment and after 200,000 units. Staphylococci and streptococci were also seen in the smear from his fluid which by this time was frankly purulent. They were not obtained on culture. He was still infected on evacuation on the 14th day, although he was given another 100,000 units.

CASE 53 — H.T. A sterile purulent effusion which on the 4th day and after 500,000 units, 450,000 of which had been given before admission, showed a growth of penicillin sensitive streptococcus viridans. A further 450,000 units failed to eradicate the infection, but appeared to destroy the haemolytic activity of the organism. It is, of course, possible that this was a different organism, but it was still sensitive.

CASE 61 — H.P.S. This case did not become infected until the 11th day when a coliform bacillus was found in small numbers. This was the last examination before his evacuation. He had received 25,000 units.

TABLE II

Case No.	Infecting organism	Units required to sterilise	Days in which sterility attained	Penicillin given before admission	Remarks
2	Clostridia P ?	50,000	2	150,000 I.P.	Sterile on one examination only
3	Clostridia P ?	50,000	2	400,000 I.P. 750,000 I.M.	Still sterile after 10 days.
15	St. haemolyticus P +	50,000	2	100,000 I.P.	Reinfected with coliform 6 days later
35	Proteus P —	150,000	4	0	Sterile on last examination only
52	Haemophilus P —	150,000	3	0	Sterile after 6 days
54	St. haemolyticus P +	150,000	9	150,000 I.M.	May have been sterile earlier but no specimen was examined. Still sterile 2 days later
58	St. haemolyticus P +	50,000	2	/0	Still sterile 6 days later
63	St. anhaemolyticus P ?	50,000	2	0	Still sterile 2 days later

Among the eighteen wounds found to be infected on first examination only eight could be kept for four or more days. All of these were apparently sterilised.

Table II shows the quantity of penicillin which brought about sterilisation, the length of time required and the organism concerned.

Pleural fluids were examined for the presence of penicillin on 165 occasions following intrapleural injections twenty-four to ninety-six hours previously. A few samples were tested after ninety-six hours, but none contained penicillin, and are not included in Table III which shows the results of these investigations.

TABLE III

	24 hours	48 hours	72 hours	96 hours
Penicillin present	15	87	8	1
Penicillin absent	9	34	7	4
Total tests	24	121	15	5

The majority of the tests were performed after forty-eight hours as this was the normal time interval between aspirations. Forty-eight hours appears to be the period in which penicillin may reasonably be expected to persist in bacteriostatic amounts in the average case.

When it is not found as expected the following reasons are tentatively suggested :—

1. *Loculation of the effusion.* If penicillin is injected into one cavity of a multilocular effusion, it may not diffuse through the membranous or fibrinous walls into adjoining cavities. Consequently if a loculus which has not itself been injected is examined, penicillin will not be found.

   Evidence now appears to be accumulating that intra-pleural penicillin increases the fibrinous material present and possibly the number of adhesions. This has not been found a factor of importance in the general survey of the first part of this paper, but it is considered that the findings might have been different if constant attention had not been given to keeping the pleural cavities dry.

2. When there is severe damage to the serous lining, penicillin may be absorbed into the blood stream and excreted, consequently disappearing from the fluid.

3. It may be destroyed by insensitive penicillinase-producing organisms. Three cases showed no penicillin present when coliform bacilli were found, but it was present in bacteriostatic amounts during their absence. B. proteus occurred twice. In one, penicillin was present and in the second, absent. In two cases an insensitive staphylococcus made its appearance during treatment. Before this happened penicillin could be detected, but not afterwards.

REPORT ON CHEST WOUNDS TREATED AT No. 6 (Br.) GENERAL HOSPITAL

By Lt.-Col. H. W. Everley Jones, RAMC., Officer i/c Medical Division, No. 6 (Br.) General Hospital.

INTRODUCTION

The following is an analysis of cases of chest wounds treated at this hospital during the past nine months. Information is often incomplete owing to the difficulties encountered due to the military situation. Frequently patients have had to be evacuated to the U. K. or transferred to other hospitals at short notice before end results could be observed, and the response to follow-up cards has been negligible. On occasion the hospital has acted as a C. C. S. with consequent scanty documentation. For these reasons some cases have had to be omitted and it is necessary to view the data given below with these points in mind. The report deals mainly with the results of penicillin treatment.

MATERIAL

A total of 169 cases with chest wounds have been treated. These are tabulated as follows:—

(*a*) Uncomplicated haemothoraces	76
(*b*) Empyemata	22
(*c*) Trauma to lung	46
(*d*) Non-penetrating injuries	25

A. UNCOMPLICATED HAEMOTHORACES. These cases were all treated by repeated aspirations with the exception of two, which had a Malecot catheter introduced at a forward unit. The results in these latter were not good as a clotted haemothorax was present in each case on arrival, a few days after the tube had been withdrawn.

Of the seventy-six cases, forty-seven were given penicillin (30,000 to 50,000 units intrapleurally) after each aspiration, and the remainder (twenty-nine) had none. (A large proportion of the patients

here described were Ps. O. W. which accounts for the numbers untreated by penicillin.)

Three cases died: one penicillin treated man from gross laceration of lung by splintered ribs; one from syncope associated with blood loss ; and the other from a complicating broncho-hepatic fistula. These last two had not been treated with penicillin.

The aim of treatment, placed as we were, was to drain the pleural cavity as dry as possible before evacuation. In most cases a small pool filling up the costo-phrenic sinus remained which could not be drained by needling. To obtain this result the following number of aspirations were required:—

Number of aspirations and days:

(a) Penicillin treated cases: —

	Aspirations	over days
	4	5
	1	2
	3	6
	1	2
	3	12
	2	9
	5	14
	6	20
	2	6
	2	4
	4	8*
	5	19
	4	13
	4	7
	4	8
	5	11
	3	7
	3	11
	5	16
	3	7
	5	17
Average	3½	9½

(b) Cases without local Penicillin: —

	4	8
	5	13
	3	19
	5	13
	4	14
	3	11
	1	1
	3	9
	3	5
	1	1
	2	6
	4	25
Average	3	10

* May have developed further reactionary effusion.

Thus penicillin neither retarded nor accelerated the response to treatment.

Nineteen of the uncomplicated haemothorax cases clotted. These were divided into:—

Those treated with intra-pleural penicillin	12
Those untreated with intra-pleural penicillin	7

All these cases appeared to be examples of "fibrino-haemothorax" rather than massive coagulation.

It was estimated that the time elapsing between the date of wounding and the development of clotting averaged, in penicillin treated cases, seven days, and in those untreated by penicillin, six days.

It thus appears, from this very small series, that penicillin used intra pleurally has no effect on the clotting of a haemothorax.

Attempts to explain why some haemothoraces clot has proved futile. The complication occurred more frequently with cases later in the series, but although they arrived at the base later after wounding than did the earlier cases, their treatment has been the same. For instance, retained FBs were present in eight clotted cases, but in twenty who did not clot. The type of wound made no difference; a roughly proportionate number were sucking wounds, perforating, or penetrating in both groups. The presence of air in the chest appeared to have no bearing on the problem. No difference was noted in the delay before starting treatment in the two series.

Men with clotted haemothoraces have usually been evacuated to chest centres directly the diagnoses have been made, but recently a number of Ps. O. W. have had to be held and thoracotomy, with removal of clot, has been done in six cases. In the first three decortication of the visceral pleura only was done with a rather slow convalescence. In the last three decortication of the parietal pleura in addition has been done with better results. An attempt at suction by use of a modified Wangensteen apparatus has been used post-operatively and found helpful — one lung was fully re-expanded in five days. In all these cases penicillin, 100,000 units, was instilled into the pleural cavity at the end of the operation and no sepsis followed.

One or two cases with moderate sized haemothoraces had to be retained here and after a few weeks most of the clot had absorbed. In contrast, one P. O. W. was captured with grossly deformed "frozen" chest, the result of haemothorax six months before. It would be interesting to know how many of these cases do absorb their clots satisfactorily.

B. EMPYEMA. Twenty-two cases were complicated by intra-pleural suppuration. Of these only two had been given penicillin intra-pleurally after aspiration, the other twenty having been aspirated solely.

The reason for the infection of the two penicillin treated cases is probably the same in that both developed multi-loculated clots which could not all be reached by the instilled penicillin, so that one or more of the loculi became infected. One of these cases became infected on the 9th day after wounding, having started to clot on the 3rd day; the other showed signs of infection on the 14th day when clotting was known to have occurred by the 10th day. Removal of clot as soon as its presence is diagnosed would seem to the be ideal.

The remaining twenty were all Ps. O. W. and in many cases additional adverse factors must be considered, such as exposure, lack of speedy medical aid, etc., but this group can be sub-divided into :—

(*a*) Those who had no penicillin at any time —15 with 3 deaths.
(*b*) Those who were given penicillin intrapleurally between the time of diagnosis of empyema and operation — 5 with no deaths.

These latter five are briefly described:—

(*a*) Pyo-pneumothorax under tension. Very ill — foul gas evacuated. Culture : Strep. haem. Aspiration and instillation of penicillin alt die. Also given 500,000 units penicillin parenterally. After two days improved considerably and pus grew only coliform bacilli (scanty). In good condition when pus had thickened after ten days. Rib resection and drainage.

(*b*) Eight inches long sucking wound, twice sutured and broken down before arrival. Muscle and skin unhealthy and necrotic. Pus grew M. Flavus. Aspirated twice and penicillin instilled intrapleurally and also given parenterally (500,000 units). After two days empyema drained through wound. After one week fit for operation—muscle and skin looking healthier. Wound· sutured and held. Separate drain.

(*c*) Very ill. Clotted haemothorax infected (staph.) after one week. One large loculus found and aspirated three times and penicillin instilled on each occasion. Condition became critical (septic broncho-pneumonia), and parenteral penicillin 500,000 units given as well as sulphathiazole thirty gm. Later aspiration produced clear, blood stained fluid with a few B. coli only. Later evacuated in good condition with much of blood absorbed.

(*d*) Haemo-pneumothorax. Started to clot on 5th day. 6th day ill: infected blood (anthracoid (?) bacilli). Aspirated four times and penicillin instilled after each tap during next week. Condition at time of operation good. Rib resection and drainage. Later empyema loculated, but high swinging temperature brought to normal by running penicillin into sinus. Finally, fresh operation with decortication and slow improvement.

(*e*) Very ill. Infected haemothorax (strep. haem.) on arrival. Three aspirations folowed by penicillin instillation during next week, at end of which his condition was much improved. Rib resection and drainage.

Penicillin has proved of great value during the period preceeding operation. By its effect on the infection the condition of these patients was greatly improved before operation.

C. TRAUMA TO LUNG.

Pulmonary haematoma	11	
Pneumothorax	5	
No damage diagnosed	13	
Pulmonary collapse	4	(all basal, bilateral in two).
Pneumonia	2	
Air embolism	1	
Large F.B. in lung without haematoma	1	
Traumatic asphyxia	1	

Penicillin was used parenterally in one man with pulmonary haematoma who had severe symptoms and ran a high temperature. Infection did not ensue.

D. WOUNDS NOT PENETRATING THE PLEURA—25

In two cases of extensive superficial wounding parenteral penicillin was used and suppuration was prevented.

SUMMARY

169 cases of chest wounds are described with six deaths. Only one of the cases who died had been treated with penicillin and the extent of the damage to his lungs was such that death was inevitable. Twelve of the wounds were sucking (ten treated by penicillin and two without, both of whom died). Four were thoraco-abdominal wounds.

The use of penicillin in preventing and controlling infection in these cases is demonstrated, but follow-up has frequently not been possible. It would be interesting to know whether penicillin caused pleural thickening in the late stage and also whether secondary pleural effusion developed in those patients in whom a small residual collection of blood remained at the time of evacuation.

No account of ancillary treatment is given, but every case had a course of sulphonamide started within a very short time of wounding. The majority of the Ps.W. were anaemic on arrival and most had a haemoglobin of fifty—sixty per cent. In these cases the transfusion of two bottles of whole blood soon after arrival in hospital caused, as expected, a very marked improvement in their general condition.

Nearly all these cases were treated in a medical chest ward and acknowledgement is due to Capt. M. O'C. Drury, R A M C, who treated many of them.

Colonel S. Dolan has kindly permitted these cases to be reported.

PENICILLIN IN ABDOMINAL WOUNDS

By Brigadier A.E. Porritt, Consulting Surgeon, 21 *Army Group, and Lt. Col. G.A.G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy,* 21 *Army Group.*

Evidence that penicillin is of value in abdominal wounds is largely presumptive, but many decisions have been based on circumstantial evidence. The following facts merit consideration. Between June, 1944 and April, 1945, British and Canadian forward surgeons performed 4275 laparotomies for abdominal wounds*. In 3545 there were intraperitoneal visceral injuries, and in the remaining 730 there were extraperitoneal lesions of the kidney, pancreas, bladder, rectum or great vessels; included in the latter group are a number of cases with

RESULTS IN 5050 ABDOMINAL AND ABDOMINO-THORACIC WOUNDS OPERATED UPON IN 21 ARMY GROUP FORWARD UNITS—JUNE, 1944 TO APRIL, 1945.

Type of Case	Total Cases	Deaths	Percentage Recovery
Penetrating or perforating abdominal wounds with proved intraperitoneal visceral injuries	3545	1056	70.2
Abdominal wounds with extraperitoneal visceral or retroperitoneal vascular injuries. A number of cases in this group had intraperitoneal haemorrhage from omental, mesenteric or other vessels, but no detectable intraperitoneal visceral damage	730	72	90.1
Total abdominal wounds (both above groups)	4275	1128	73.6
Thoraco-abdominal or abdomino-thoracic wounds	775	328	57.7
GRAND TOTALS (Abdominal wounds not counted twice)	5050	1456	71.2

* Footnote: At the time of going to press the April reports of two forward surgical units had not been received.

intraperitoneal haemorrhage from mesenteric, omental or other vessels, but no detectable intraperitoneal visceral injuries. The total deaths were 1128, representing a recovery rate of 73.6 per cent. In the same period 775 operations were performed for thoraco-abdominal wounds with 328 deaths, representing a survival rate of 57.7 per cent. Therefore 5050 operations were performed for abdominal and thoraco-abdominal wounds with 1456 deaths**, giving an overall recovery rate in these serious injuries of 71.2 per cent. These facts may be tabulated (See previous page).

These were not selected cases. It was the rule here, as it was in the Desert, that no man was denied the chance offered by operation however hopeless his apparent condition, and if one surgeon lacked the time or the desire to tackle a case a colleague had both. Some amazing recoveries resulted from this policy, but it is clear that the operative mortality must be greater than in series of selected cases where the desperately wounded are left to their fate.

Equally favourable figures have not been reported before from British sources in any large series of cases operated upon by many different surgeons, and while many men must have died after evacuation of complications directly attributable to their wounds, it is probable the final recovery rate will be significantly better than any previously recorded figures. We suggest that the prevention or control of many infective complications by penicillin is the possible reason. Such complications always account for a proportion of the deaths occurring after the first few dangerous days when the mortality is greatest. Ogilvie states that deaths after the third day are mainly due to sepsis.

Certain figures from other campaigns may be given, but comparison cannot be exact because in the cases recorded below the "follow-up" in most cases was more prolonged and the final percentage is therefore lower for this reason. Owing to the proximity of this theatre to England evacuation was relatively easy, and in the majority our "follow-up" does not extend beyond fourteen days. Despite this it is improbable that the gap would be completely bridged by late deaths occurring after evacuation.

	Total Cases	Deaths	Percentage Recovery
Ogilvie (M. E. F.)	628	246	60.8
Lowdon (M. E. F. and C. M. F.)	64	28	56.2
Edwards (C. M. F.)	640	301	52.9
Edwards (C. M. F.)	640	267	58.3

** All deaths occurring before evacuation to the U. K. are accounted for, whether they occurred in the original unit, in residues left behind in the care of a following unit, or in hospitals.

Two separate sets of figures are given for the C.M.F. because thirty-four men died after the tenth day, and to provide a fairer comparison with the B.L.A. figures these deaths have been excluded in the second set.

It is interesting to recall that in the Great War less than fifty per cent of men with abdominal wounds recovered, and Till states that only 31.6 per cent of cases operated upon by German surgeons on the East and West fronts during 1942-43 survived.

In making comparisons all possible factors influencing the results should be evaluated, and the more important of these will now be considered.

TIME AND DISTANCE

We have stated elsewhere that from the time of Alamein in 1942 onwards all the big battles producing the largest numbers of casualties have been initiated from established positions. The earliest and costliest phases have approximated to static warfare with the surgical cover well forward and well placed, and early surgical attention was facilitated by the formation and increasing use of field surgical units. With the possible exception of Sicily these remarks are generally applicable.

There have been combined operations where this was not so. Except on a small scale these were not features of the M.E.F. campaigns, but they became more common in the C.M.F. None, however, was as large as the Normandy invasion, and none more difficult or dangerous than the Walcheren episode.

Within limits the sooner any abdominal catastrophe is dealt with the better the results will be. Many figures relating to perforated ulcers and appendices have been published in support of this, and Lowdon, Aylett, Edwards and others have shown the same thing occurs in abdominal wounds. Have these intervals changed greatly in this as compared with previous campaigns? Lowdon working in an F.S.U. with the Eighth Army gives the average time interval in fifty-eight cases as 15.4 hours, and this included a number of cases operated upon in Sicily where transport in forward areas was sometimes unusually difficult. Aylett working in an F.S.U. in the B.L.A. gives figures showing the average time interval in fifty-four cases was 14.4 hours. Edwards states: "of 450 wounded and helpless patients (in Italy), 309 were brought to operation within twelve hours, and 373 within eighteen hours. A large number of the remaining seventy-seven were prisoners, the collection of whom obviously involves delay". The average time between wounding and commencement of operation was worked out for 200 abdominal cases in 21 Army Group and was found to be 13.1 hours; to avoid getting a false impression a number of paratroop and prisoner cases operated upon 2—3 days or more after wounding were deliberately excluded

in making this calculation. Clearly the time intervals in this theatre show no significant variation as compared with those in other campaigns.

Actually short lines and rapid evacuation produce an effect opposite to the one that might be anticipated. A larger number of desperate cases survive until they can receive resuscitation and operation, and naturally these more severe cases show a higher post-operative mortality. When the evacuation is long and difficult many of these, as Lowdon remarks, are eliminated by a process of natural selection; they fail to reach the surgeon. Thus a short and easy line of evacuation reduces the total abdominal mortality and tends to increase the actual operative mortality.

PRE-OPERATIVE TREATMENT

The importance of adequate resuscitation has been recognised and effectively carried out from the M.E. campaigns onwards. The methods in common use here correspond closely to those recommended by Major General W.H. Ogilvie and Colonel J.S.K. Boyd in various official M.E. memoranda and to those detailed in the War Office publication on "Resuscitation". The same officer, Lt. Col. G.A.H. Buttle, who was mainly responsible for the extremely efficient resuscitation services in the M.E.F. has performed similar functions in the B.L.A. The resuscitation and transfusion services have earned an enviable and probably unequalled reputation in the RAMC, but the magnificent work done by the pioneer field transfusion units in the Desert has not been excelled by any done here.

ANAESTHESIA

No special methods are in general use not equally available in other theatres. General anaesthesia is used more often than local methods and induction is frequently by Pentothal. A few highly skilled anaesthetists (see joint article by Aylett and Alsop) give continuous Pentothal alone, but the majority carry on with N_2O, O_2, and ether given by a Boyle's apparatus, or ether given by an Oxford Vaporizer. Cyclopropane was seldom employed owing to lack of supplies and facilities for administration—although portable Heidbrink machines were available latterly.

OPERATIVE TREATMENT

A brief outline will be given of the procedures commonly employed, and it will be seen that they too conform closely to those practised in earlier campaigns (Ogilvie, Lowdon). Some surgeons have their own ways of doing this or that, but there has been no major departure or advance in surgical technique to account for the improved results.

Most forward surgeons regard no abdominal case as hopeless unless he is dead, and they are aware of the potential dangers of any wound between the nipples and the knees, and the especial risk of missing abdominal injuries in men with buttock wounds.

The abdomen is explored by extending the original wound, or more often through a separate paramedian or rectus splitting incision affording better access; transverse incisions are not popular but oblique incisions are used to expose damaged structures in the flanks. A systematic s·arch is made for lesions and these are dealt with in the appropriate manner. Blood and extravasated fluid are removed by aspiration and gentle swabbing.

Tears in the stomach and small intestines are sutured if possible, and resections are shunned unless the damage to the viscus or its blood supply renders this course unavoidable. Small gut enterostomies are frowned upon as primary procedures, although they may be resorted to as a desperate remedy in postoperative ileus or obstruction. On the other hand exteriorisation of large bowel injuries is regarded as the treatment of choice, and if necessary the part is mobilised to enable this to be done with ease; resections are avoided unless the injuries are multiple and adjacent or the damage extensive. Colostomies are formed in men with lower sigmoid, rectal and anal injuries, and attempts made to close the tears in these relatively fixed parts. Some surgeons close small or retroperitoneal wounds of the caecum or ascending colon, drain the area, and perform a safety-valve caecostomy. But there are few exceptions to the general rule that the safest measure in colonic injuries is to exteriorise the damaged area.

Bleeding vessels are ligatured, and haemorrhage from a solid viscus like the liver is treated by suture or, if this is unsuccessful, by packing; if this latter step is necessary many surgeons follow Ogilvie's advice and try to separate the pack from the actual liver substance with a layer of omentum. Fibrin foam has only been tried on a very limited scale because of lack of supplies. Raw areas on the omentum, mesenteries, etc., are peritonealised if possible. A damaged spleen is removed, and many surgeons have confirmed that splenectomy can be performed with ease through the chest in thoraco-abdominal wounds. A disintegrated kidney is excised, but the organ is preserved if the lesion is not extensive. Wounds of the pancreas are often associated with lesions of the great vessels, duodenum and coeliac plexus, and men with such serious injuries seldom survive long enough to reach the surgeon. In the few who do it is wise to insert a drain down to the site of pancreatic damage and leave this for 3—4 days until a track has been established. The subsequent fistula may prove troublesome for a time but tends to close naturally if the main ducts are not blocked. Bladder wounds are treated by suture and suprapubic cystostomy. All areas where blood or exudate might collect are drained.

POST-OPERATIVE TREATMENT

It is realised that the surgeon whose interest begins and ends in the operating theatre would be more safely employed as the unit carpenter, and adequate post-operative care is regarded as essential. In practice the ideal was not always attainable, largely because the staffs of casualty clearing stations and advanced surgical centres are inadequate to cope with large rushes of cases. The available medical and nursing officers and orderlies performed prodigies during the big offensives, yet there is a limit to human endurance and only twenty-four hours in one day.

But there have been no departures from accepted practice in the actual treatment. Routine gastric suction; adequate intravenous fluids; administration of fluids, jellies and purees by mouth at a relatively early stage; a holding policy of ten days; and the various other general measures of nursing care, reassurance, relief of pain, etc., practised here were all based on experience gained in other theatres of war. Most patients were nursed in the half-sitting position, but a number of Canadian surgeons kept their patients lying flat and found that many men preferred this position. Many Canadians also dispensed with pyjamas or bed jackets in the more helpless patients as this facilitated nursing and increased the patients' comfort.

DIET, CLIMATE, TERRAIN, MISSILES AND NATURE OF WOUNDS

We have discussed these factors already in "Factors Influencing the Occurrence of Infection in War Wounds" and the observations need not be repeated.

CHEMOTHERAPY

Sulphonamides intravenously or by mouth were used less commonly in this theatre than in the M.E., and some surgeons used none at all, rather preferring penicillin as being a much safer drug.

Ogilvie presented suggestive evidence that intraperitoneal sulphadiazine is of value in abdominal wounds. For the first seven months in the B.L.A. the supplies of sulphadiazine or sulphamezathine in a form suitable for intraperitoneal use were negligible, and relatively few men received them. Therefore if they are beneficial this lack should have prejudiced the results. Sulphadiazine suspensions became generally available from January, 1945 onwards, and then many surgeons exploited them. The overall recovery rate for January to April was 74.3 per cent, somewhat higher than the average (73.6 per cent), and this tends to support the view that sulphadiazine is beneficial. Part of the improvement, however, may be explained by increasing surgical experience and skill, evidenced particularly in the case of thoraco-abdominal wounds where the recovery rate rose

more or less steadily from thirty-three per cent in June, 1944, to about sixty-seven per cent in the later months of the campaign. In parenthesis it should be stated that the majority of our surgeons had no previous experience of forward surgery before D-day. The recovery rates in men with abdominal wounds have shown no such wide variation, but with few exceptions the general trend has been upwards as the following figures show:—

June	69.0 per cent	October	75.6 per cent	February	71.4 per cent
July	70.3 per cent	November	78.7 per cent	March	77.2 per cent
August	71.8 per cent	December	79.4 per cent	April	79.6 per cent
September	75.6 per cent	January	75.0 per cent		

Penicillin: This is the one really new factor as it has been used for the first time as part of the routine treatment. In the earliest days of the campaign this was not so, or the penicillin was given for some other reason, but soon its use became almost universal as many surgeons gained the firm impression that it was of value.

Most of the penicillin was given by continuous intramuscular drip (100,000 units in 500—540 ccs. normal saline every day for 7—10 days), and only a few surgeons used it locally in the peritoneum—although local applications should be of value in those cases where sensitive organisms are not completely overshadowed by insensitive penicillinase-producing types.

Several critics have stated that systemic penicillin is valueless in abdominal wounds as the drug cannot pass the peritoneal barrier. This is incorrect as is shown by observations recorded in other articles by Hughes, Foster and Colquhoun and Heatley. The level in peritoneal exudates may be lower than in the blood, although not invariably so, but in any case peritonitis and subphrenic abscess are not the only possible infective complications of abdominal and abdomino-thoracic wounds. Retroperitoneal and pelvic cellulitis, intra-mesenteric suppuration (we know of two cases occurring last June where the patients died of ileus and where at post-mortem abscesses were found between the layers of the mesentery), portal pyaemia, parotitis, mediastinitis and pulmonary infections, etc., are all possibilities, and many of these are probably due to penicillin-sensitive organisms. It is assumed too readily, and as far as we can discover without good evidence, that the complications following visceral injuries are mainly due to col.form and enterococcal types insensitive to penicillin.

Direct proof that infective complications were less common is difficult to obtain, but there is certain suggestive evidence. Many post-mortems were performed and in a considerable proportion evidences of infection were slight or absent, and this in cases where it was almost to be expected. The incidence of chest complications was very low even in the upper abdominal and thoraco-abdominal cases and infections such as parotitis non-existent in penicillin treated

cases. A much higher proportion of clean healing was achieved in laparotomy wounds than any with previous experience had ever been accustomed to see, and it is probable that an agent producing such beneficial effects superficially is not inactive in the depths. In this respect the following remarks quoted from a D.O. letter from the Consulting Surgeon, A.F.H.Q., dated 5 h August, 1944, and entitled "The Trend of Surgery in Italy" are of interest:—

> "It is confirmed that continued sepsis of the laparotomy wound is usually related to trouble inside the peritoneal cavity. Thus eighteen sepsis-free cases out of forty admissions to one hospital went forward quickly to a full recovery. In fourteen others, there was sepsis of varied degree in the laparotomy wound and convalescence was marred by incidents. Five of these needed second operations, e.g. drainage of abscess. Two died, both from sepsis or its sequelae. This high incidence of sepsis in laparotomy wounds is not surprising considering the need for colostomies and the type of surgery generally. . . . . . . A factor of major importance that has been confirmed is the great vulnerability of retroperitoneal tissues to infection".

In the earlier stages of this war suppuration in laparotomy wounds was commonplace, and in the Medical History of the Great War we read: "Suppuration in the abdominal wound was always a trouble, and the resulting poor scar was one of the principal reasons for placing men in the lower categories". Burst abdomens and septic wounds were not unknown in the B.L.A., but a high proportion of laparotomy wounds healed by first intention or with only slight evidence of infection.

Repeated attemps have been made since June, 1944, to determine the bacteriology of the peritoneal exudates and of any infective complications. These have been almost entirely unsuccessful because, owing to combinations of circumstances, it has never been possible to have one of the few available mobile laboratories working alongside field units at the proper times; or if they were, the pathologist had so many throat swabs and bloods to examine that he could not spare the time to carry out additional investigations. We only have information about cultures from twenty-six cases (seventeen aerobic and anaerobic and nine aerobic only), and about direct films from ten others examined in the forward areas where no culture facilities were available. The latter, of course, supplied no information of real value, and they usually showed mixtures of cocci and bacilli that could not be identified with certainty. The twenty-six cultures gave coliforms in fifteen cases, staphylococci in six, strept. faecalis in five, strept. viridans in three, strept. haemolyticus in one, Cl. welchii in five, Cl. sporogenes in two, Cl. bifermentans in one, B. subtilis in three, B. proteus in two, and a number of unidentified cocci and bacilli. The swabs for these cultures were all taken at the time of

operation, and it would be very interesting to learn the bacteriology of any infective complications developing in cases treated with and without penicillin. Unfortunately we can supply no information on this point.

CONCLUSION

In a very large number of abdominal cases operated upon by many different surgeons the recovery rate has been more favourable than usual. Factors influencing the results have been discussed, and it is suggested that the almost universal use of penicillin may have prevented or controlled many infective complications. These always account for a proportion of the deaths occurring after the first few dangerous days when the mortality is greatest.

REFERENCES

AYLETT, S. O. and ALSOP, A. F. (1945), Brit. Med. J., I, 547.

EDWARDS, H. C. (1944), "Statistical Report on 640 Battle Casualties operated on in the Forward Area, C. M. F. for Abdominal and Abdomino-Thoracic Wounds" (Circulated by Consulting Surgeon to War Office, Jan., 45).

LOWDON, A. G. R. (1944), Edinb. Med. J., LI, 257.

OGILVIE, W. H. (1944), Surg. Gynec. Obst., LXXVIII, 225

TILL, A. S. "Review of Publications from the Surgical Research Unit of the OKH 1942—3".

Apart from the Medical History of the Great War all other references (HUGHES, FOSTER and COLQUHOUN, and HEATLEY) are to articles in this brochure.

THE USE OF PENICILLIN IN CERTAIN DISEASES OF THE EAR, NOSE AND THROAT

By Lt.-Col. J. P. Stewart, RAMC, Adviser in Otorhinolaryngology, 21 Army Group

The following notes are compiled on the understanding that where penicillin is administered either locally or by injection the causal organism is penicillin sensitive. There are, of course, a number of cases especially in the chronic forms where a mixed type of infection is present and it may be impossible to isolate a penicillin sensitive organism because of the profuse overgrowth of the more vegetative types, and the exhibition of penicillin in such cases might be responsible for a slight improvement in the clinical picture. On the whole, however, one has found the use of penicillin in the chronic infections to be disappointing.

EAR

Otitis Externa: Penicillin cream (Lanette wax, 12gms.; Arachis oil, 28gms.; aq. dest. ad 100gms. with 500 units of penicillin to each gram) applied on ribbon gauze has been used in the treatment of a large number of cases of otitis externa. It clears up this irritative skin condition in roughly 50% of the cases. It has no advantages over the better known methods of treatment, but it has a definite place in the therapeutic armamentarium for this condition. The cream has been found to be superior to the aqueous drops, probably because of its additional mechanical soothing effects on the inflamed epithilium lining the external auditory meatus.

Furunculosis: Treatment is the same as in the above condition, but if the furuncles are recurrent or resistant to the local treatment the penicillin should also be administered by the intramuscular route.

Acute Suppurative Otitis Media: Some observers report good results when penicillin in aqueous drops is instilled into the middle ear in an acute suppuration. A sample of pus from the middle ear should be taken for examination, either on spontaneous or

artificial rupture of the drumhead. The best results are obtained where the local treatment by penicillin is supplemented by parenteral injections, and as more penicillin becomes available this will become the standard form of treatment in the initial stages of an acute infection of the middle ear.

Chronic Suppurative Otitis Media: Penicillin introduced into the middle ear by whatever vehicle has proved most disappointing in its results. It has absolutely no beneficial action on granulations, polypi or cholesteatoma. After the radical mastoid operation, a penicillin gauze pack for the operation cavity has been used, but as the first dressing is not carried out for four days following, the effects of penicillin had long since worn off, and such a procedure has been entirely given up.

Intracranial Complications: We have in penicillin a very powerful agent in the treatment of these cases. Excellent results have been obtained in septic thrombosis of the lateral sinus, and the mortality rate of this disease has been considerably reduced by the use of penicillin. Again it is emphasised that no haphazard employment of penicillin should be embarked upon until the bacteriologist has given his opinion on the results obtained from a blood culture and a direct smear from the mastoid operation cavity taken at the initial operation.

Meningitis: Otitic meningitis is often fatal, and treatment by penicillin should be instigated at once and prosecuted with the utmost vigour as soon as the condition is diagnosed or even suspected. It is quite justifiable to commence treatment prior to obtaining the bacteriologist's findings, and one should never wait for a positive finding for organisms in the cerebrospinal fluid as in the vast majority of cases organisms only appear in this fluid in the terminal stages when therapeutic, or indeed any, intervention is too late to be of the least value. The penicillin can be administered by a continuous intramuscular drip or by intermittent injections, and as the treatment of this type of meningitis is carried out in part by cisternal puncture, a reduced amount in bulk penicillin is run into the cisterna magna on performance of this manoeuvre.

Brain Abscess (cerebellar and temporal lobe): One can only speak from the experience of two cases of brain abscess treated by the combination of penicillin and operation, but one has had a considerable experience in the treatment of brain abscess by operation prior to the penicillin era. It is appreciated by most that when an abscess in the brain becomes walled off and encapsulated effective surgical drainage contributes towards a favourable outcome; but in those cases of abscess, without any definite encapsulation, and where they are surrounded by an area of red degeneration, the end results by operation and evacuation of the abscess contents are often most disappointing. It is in this last group of cases that

penicillin is invaluable. At the moment the writer is treating a case of cerebellar abscess in which these conditions (non-encapsulation) are present, and from past experience one would have no hesitation in saying that this case would have terminated fatally a week ago, but at the time of writing progress has been, and is, most satisfactory. Penicillin given by intramuscular continuous drip has been employed, and one is extremely optimistic of a favourable result.

NOSE

Acute Rhinitis: Penicillin in the form of a snuff, or in drops or in a spray, is said to mitigate the more violent manifestation of the "common cold", but the writer has no personal experience of this form of treatment.

Furunculosis: Furunculosis of the nose is at times liable to produce fatal complications owing to an extension of an infected embolus from the primary lesion into the cavernous sinus. In all such cases penicillin should be employed as a routine both in prophylaxis and therapy.

Post-operative use in nose: After septal operations or the removal of polypi healing is accelerated by the local application of penicillin employed either as a cream or in a spray (aqueous or oily). In the majority of such cases a mild organismal infection of the soft tissues takes place 24 hours after operation, manifested by oedema and swelling of these tissues, accompanied by a mucopurulent discharge, and it is to combat this that penicillin is employed.

Paranasal Sinus Disease: Briefly the same principle in treatment by penicillin holds good for these cavities as for those of the middle ear spaces. The acute cases respond well, while little or no change occurs in the chronic case. Antral infections being the most common, the procedure is detailed. Under aseptic conditions a proof puncture of the suspected antrum is undertaken, and if pus is present a sample is collected and sent for examination. After the irrigating fluid has been expelled from the antrum 5ccs. of penicillin in tragacanth solution is injected into the antral cavity (500 units of penicillin to 1cc. of half strength tragacanth solution BP). Tragacanth has been found a very suitable medium for the penicillin as it is retained in the antrum for some time after an ordinary solution would have been got rid of by the natural drainage, and this prolongs the action of penicillin on the affected mucosal lining. The antrum is washed out every second day and fresh penicillin-tragacanth solution injected as above. It is worth while carrying this out for 5 or 6 treatments, and the results obtained are very encouraging.

A similar procedure can be carried out on infections of the sphenoidal sinus, while Proetz's displacement treatment should be employed for infections of the ethmoidal and frontal sinuses, using an aqueous solution of penicillin of the same strength.

On the conclusion of an operation for drainage on any of the paranasal sinuses it is the writer's practice to pack these cavities with ribbon gauze soaked in penicillin solution and to leave this in situ for 24 hours. Post-operative healing has been greatly accelerated.

Intracranial Complications: So far the limited number of cases of cavernous sinus thrombosis encountered by the writer have responded most favourably to penicillin. In pre-penicillin days a complication of this nature was almost invariably fatal, and those that did recover generally found their way into the literature as cases of rarity. Again the treatment must be instituted without delay and carried out with vigour and intensity. The writer has not yet had the opportunity of treating an abscess of the frontal lobe with penicillin as part of the treatment.

THROAT

Tonsillitis: In severe cases of tonsillitis accompanied by high temperature, penicillin treatment has become empiric. It hastens recovery, lessens the risk of a spread of the infection to the adjacent tissues, and minimises the risk of peri-tonsillar abscess formation. A peri-tonsillar abscess when present must be evacuated—penicillin therapy will not clear up such an abscess per se. Lozenges of penicillin are not very useful in the acute stages of tonsillitis and penicillin is best exhibited by the injection method.

Post Tonsillectomy: Following tonsillectomy penicillin lozenges are of value and should be used as a routine. The traumatised tissues of the tonsil bed become mildly infected in the same way as the soft tissues of the internal nose after an operation, and useful results in both the comfort of the patient and reduction in the swelling of the tissues are obtained. Again, during epidemics of sore throats the use of penicillin lozenges is advocated from the prophylactic point of view.

Vincent's Infection: Vincent's infection of the tonsil responds most favourably to penicillin, preferably given by injection. It is not, however, in any way superior to the more common mode of treatment by the intravenous injection of Neo-Salvarsan, though of course one must remember that in rare instances unpleasant sequelae may result from the use of arsenicals.

Acute Laryngitis: Penicillin is indicated in cases of acute laryngitis and septic oedema of the larynx.

Gunshot wounds of neck and foreign bodies in neck tissues: After the removal of shrapnel, etc., from the deep tissues of the neck it has been the writer's invariable practice to irrigate the wound with penicillin and then to pack the wound with gauze lightly wrung out with penicillin solution. The results have been admirable as regards the prevention of local sepsis.

In conclusion one would say that penicillin therapy in certain diseases of the Ear, Nose and Throat is most valuable. The results obtained in the chronic types of infection are no better, and in the majority of cases not as good, as those obtained by the ordinary methods of treatment.

PENICILLIN IN MEDICINE

By Brigadier Ernest Bulmer, Consulting Physician, 21 Army Group

In the early months of the campaign penicillin supplies were earmarked for surgical use and were inadequate to allow treatment of any but special medical cases. As soon as supplies became adequate, however, extensive use was made of it in medical cases, especially as saving of man-power is so urgent a problem.

VENEREAL DISEASE

Penicillin had an obvious application to the treatment of venereal disease, and Lt.-Col. D. J. Campbell early used it as the standard treatment of gonorrhœa, abandoning the sulphonamides; the 24-hour treatment of this disease at strategically placed centres in Corps and L of C effected a huge saving of man-days, and produced a cure rate of about 98%, a very creditable result. At a later date penicillin was applied to the treatment of primary syphilis. It would be wise to suspend judgment until some years have elapsed, but at present it would seem to be the drug of choice in the primary sero-negative phase; in primary sero-positive cases and in secondary cases the American results have not been very good, and specific chemotherapy in addition will probably be needed.

DERMATOLOGY

Lt.-Col. F. F. Hellier made equally full use of penicillin in the dermatological cases; at first a supply of penicillin which was unsuitable for injection was made available to him and was distributed as far forward as divisional FDSs; later stocks became adequate for all dermatological needs. Penicillin in dermatology is harmless (at least in any but the most exceptional person), and this at once singles it out from the sulphonamide group which has caused many sensitisation dermatoses. It is economical to use and as a spray of 500 units per cc. is effective. Its use in the simple pyodermias has lead to a great reduction in the period of hospitalisation, and in impetigo especially has saved many days per patient.

GINGIVITIS

An unexpected application of penicillin was to the treatment of acute ulcerative gingivitis. With the co-operation of the DDDS, Col. H. J. Higgins, Maj. A. State, AD Corps, and Maj. J. Hart-Mercer have been carrying on an extensive investigation at 75 (Br.) General Hospital, where a ward was placed at their disposal. Their main conclusions can be read elsewhere in this brochure, but there is no doubt that local treatment with lozenges or spray is simple and effective and more economical than parenteral treatment.

The results of another investigation of the same type carried out by Maj. Powell, AD Corps, and Capt. Colquhoun at 105 (Br.) General Hospital are also reported in this brochure.

DIPHTHERIA

In diphtheria the results of penicillin treatment have been disappointing. In the acute phase it was hoped that the drug would exercise a rapid bacteriological action on the C. diphtheriæ but there has been no convincing evidence of this. Convalescent carriers were concentrated at 110 (Br.) General Hospital, and controlled experiments were carried out by Lt.-Col. R. E. Tunbridge with the help of Majs. J. H. H. Keall and J. V. Dacie. No effect on the carrier state could be demonstrated either with penicillin spray or lozenges, and recourse had to be had to tonsillectomy; sections of the tonsils showed the organisms deeply buried in unhealthy crypts, and presumably inaccessible either from the mouth or from the blood stream.

MENINGITIS

At 111 (Br.) General Hospital, Lt.-Col. McArdle and Maj. R. J. G. Morrison treated a small series of cases of meningococcal meningitis with intrathecal and parenteral penicillin without sulpha drugs. The drug was effective, but the repeated lumbar punctures I regard as dangerous owing to the risk of introducing a resistant organism into the theca. It would seem reasonable to inject penicillin intrathecally at the time of the diagnostic lumbar puncture if the fluid is turbid; in pneumococcal cases especially the delay in examining the fluid and then having to do a second lumbar puncture would be avoided.

SEPTICÆMIA

Many cases of septicæmia have been treated, usually with good results; unfortunately no single hospital has had enough

cases to produce a convincing series, but this application of the drug is sufficiently well known, and further proof is not needed. In the very severe septicæmias, however, the correct dosage of penicillin has yet to be determined and the correct level to be maintained in the blood. Should a constant level be maintained by continuous intra-muscular drip? Is it preferable to produce intermittent high titres by discontinuous three-hourly injections? This is not known, but I have been most interested in a few cases resisting both of these methods which responded to "blitz" treatment (Lt.-Col. C. L. Cope, 79 (Br.) General Hospital), the daily dose being given over a period of two hours at quarter-hourly intervals.

TYPHOID

Maj. R. Winston Evans, of 108 (Br.) General Hospital, has demonstrated the sensitivity of B. typhosus to penicillin in very high titres. There have been few cases of the disease lately to whom this discovery could be applied; in the few to whom huge doses have been given the results have been disappointing, but the subject should be pursued.

WEIL'S DISEASE

There has been practically no Weil's disease since we left the beach-head, so that the observations made there cannot be enlarged.

CIVILIAN USE

Penicillin has considerable applications to medical treatment. In civil life its use will be limited to those who can go into a hospital or nursing home for the tedious injections; outside of such institutions doubtless much penicillin will be used by external application or local oral use. It is hoped that some other method of administration may be found; Lt.-Col. D. J. Campbell and his associates have had interesting results with a slow release medium in gonorrhœa, but if supplies become really adequate and cheap, oral administration may be possible. In venereal disease it is doubtful how many civilians could absent themselves for 24 hours in the case of gonorrhœa or eight days in the case of syphilis for penicillin treatment. It would be impossible for most to produce a convincing "cover" plan to explain where they had gone and why!

INHALATION

The administration of penicillin by inhalation may be a practicable method, both for its local and general effects. Research

on this aspect was projected, but a suitable inhaler could not be obtained for the theatre.

CONCLUSION

It may be said that penicillin would be the drug of choice in many diseases were it not for its rather impracticable method of administration. Sulphonamides must remain the first line of attack under the conditions prevailing in civil life, but the local treatment of skin and mouth infections can be readily used in the home and severe infections will have to be sent into institutions.

I would add that the articles on penicillin in medical conditions do not represent fairly the great deal of careful work that has been done on this subject by the physicians of the Army Group. In the rush of work even routine documentation has often had to suffer, and many have left the collation of their penicillin results until they had time to study them at leisure.

PENICILLIN IN DERMATOLOGICAL CONDITIONS

By Lt.-Col. F. F. Hellier, RAMC, Adviser in Dermatology, 21 Army Group

Penicillin has been of great value in the treatment of infections of the skin and has been used on an increasing scale as more penicillin has become available, until eventually it was being employed as far forward as FDSs. It has been used locally for the most part though sometimes parenterally for deeper infections.

METHOD

Both a solution and an emulsion of penicillin have been employed. The advantages of a solution, sprayed on the skin, are the speed and simplicity of treatment and the lack of danger of cross infection: it is also very easy to prepare small quantities of solution by dropping a tablet (5000-10,000 units) into 25-ccs of sterile water. The disadvantage is the necessity for a spray which is apt to wear out quickly in a busy clinic and is not available for the Unit MO. Further the solution should be sprayed on three times a day which is difficult in out-patients. The advantage of the emulsion is that the soldier need not attend the clinic for spraying, but the emulsion is less easily prepared. Originally much importance was attached to the deterioration of the penicillin which was more rapid in emulsion than in solution. Recently, however, Hughes* has shown that the modern penicillin is more stable, and even at room temperature the emulsion only loses about 30% of its activity in 14 days; if kept in a refrigerator it loses about 30% in 80 days.

The solution used has contained from 200-500 units penicillin per cc: weaker than this it gives a larger number of failures but a stronger solution does not seem to be any more effective. The emulsion has been made up with 30% Lanette wax in water in a strength of 200-500 units penicillin per gm. Spraying has been done three times a day; more frequent applications do not seem to give any better results.

* See report by Major K. E. A. Hughes on "Stability of Penicillin".

IMPETIGO

Impetigo clears rapidly with penicillin, so much so that if a patient is not almost clear in 5-7 days, it is unlikely that he will respond to penicillin and the treatment should be changed. It was soon found that if the patients were discharged as soon as the skin was clear many of them relapsed. Our practice has, therefore, been to retain the patients for a further 48 hours after the crusts have fallen off and to apply a mild antiseptic such as 2% Hydrarg. Ammon. in Lassar's paste or Eau d'Alibour. The following results in a series of cases of impetigo were obtained in one hospital and are almost exactly similar to those obtained in several other centres. All the cases were typical impetigo, many very severe, but those showing complications such as otitis media or seborrhœic dermatitis were excluded. No control series are available in BLA but the results are given of a series of 100 cases treated by sulphathiazole (5% in emulsion) in the UK, and also a very large series treated by numerous dermatologists in the UK with microcrystalline sulphathiazole:—

TREATMENT OF IMPETIGO

	No. of cases	Failures	Av. time of cure	Treatment
BLA.	141	9 (6.3%)	8.5 days	Penicillin spray
UK (FFH)	100	—	13.7 days	5% sulphathiazole
UK. (various)	6000 +	11%	11.3 days	Microcryst. sulphathiazole

In an attempt to reduce the number of failures a further series were treated, in conjunction with Maj. G. A. Hodgson, with a solution containing penicillin (500 units per cc) and "Merthiolate"" (1 in 1000); Maj. Hughes kindly investigated the mixture and showed that it only deteriorated slightly more rapidly than penicillin alone.

IMPETIGO TREATED WITH PENICILLIN AND "MERTHIOLATE"

	No. of cases	Failures	Av. time of cure
F. F. H.	31	3	7.4
G. A. H.	54	7	6.7
Total	85	10	6.9

The failures were no fewer than with penicillin alone. This seemed to indicate that the cause of failure lay more with the patient than the organism. This was supported by the observation that the failures often resisted other forms of treatment. There was often a history of previous attacks and a tendency to recur, and the lesions tended to affect the eyebrows, ears, scalp, etc.—in other words, the seborrhoeic sites. The importance of the seborrhoeic background in the occurrence, course and prognosis of impetigo and impetigo-like lesions has impressed all the dermatologists in BLA.

ECTHYMA

This condition is very common on the legs of soldiers and also affects the arms and is usually difficult to cure consistently quickly, although many cases undoubtedly clear rapidly on admission to hospital. Our treatment has been to wash the legs daily with soap and water and to spray three times a day with penicillin for about six days; when the ulcers are clean a bland application like Lassar's paste or codliver oil ointment is applied. The following is a series of 45 consecutive cases treated in one hospital:—

Evacuated in an emergency on their 7th and 11th days	2
Returned to duty	43
Average time of cure (43 cases) ...	12.3 days
Average time on penicillin treatment ...	6.1 days
Average time for cases treated in UK in 1943	30.1 days

SYCOSIS BARBAE

The immediate results with penicillin have been excellent. We have used sprays mostly, usually for slightly longer than with impetigo, after which we have changed to Ung. Quinolor Co. Some cases, especially out-patients, have been treated with penicillin emulsion with equally good results. The following series of 27 cases were all treated with penicillin spray; all had a history of three months or over. Those discharged to duty were all free from pustules and the skin apparently normal except in a few cases where there was some slight redness.

Sycosis Barbae treated with penicillin spray

Total cases	27
Evacuated to UK	2
Transferred to another hospital for ENT treatment	3
Evacuated to another hospital in an emergency	3

Returned to Unit, apparently cured...	19
Average time of cure (19 cases) ...	15.4 days
Average time of hospitalisation in UK in 1943	36.2 days

These results are superior to any I have obtained previously, and many soldiers have declared after a few days' treatment that they were better than they had been for many months. I do not know how many of these cases relapsed after discharge, but as a preventive all were provided with Ung. Quinolor or penicillin emulsion to use for some weeks after leaving the hospital.

BOILS

We cannot give statistical evidence of any value in a condition so variable as boils. Our general impression is that penicillin used externally does not affect a real boil, though it will clear the superficial folliculitis seen round boils or where a plaster has been applied, etc. Parenteral penicillin, using 20,000 units three-hourly up to a total of about 500,000 units, will often cut short an attack of boils and is particularly useful in severe boils of the neck. It sometimes cures recurrent boils but may fail.

In carbuncles the results are often dramatic, pain being greatly relieved in 24 hours, but the carbuncle still takes a considerable time to heal. Even after very large doses (1-2 million units) fresh carbuncles may occur in a matter of a few weeks.

INFECTED DERMATITIS, SEBORRHOEIC DERMATITIS, Etc.

Penicillin used locally either as a spray or as an emulsion has a definite place in the treatment of these conditions. It is important to realise, however, that it will only deal with the infective element. Usually there is a marked improvement during the first few days, and then the condition becomes stationary, and one has to change to some application suitable to the underlying dermatitis. Prolonged use of penicillin after the initial improvement may even lead to the production of penicillin resistant strains of organisms. In severely infected pompholyx or seborrhoeic dermatitis in which there is evidence of deeper inflammation with, for example, redness and tense swelling of the ears, penicillin is often helpful, especially if there is any suggestion that the patient is sulphonamide sensitive. We have usually given about 500,000 units penicillin in three-hourly injections of 20,000 units.

SUMMARY

1. Penicillin has been used as a spray and as an emulsion with good results in skin infections (strength 200-500 units per cc. or gm. respectively).

2. Using a spray followed by two days of mild antiseptic, 140 cases of impetigo were cured in 8.4 days with seven failures.

3. 19 out of 27 cases of sycosis barbae were discharged in 15.4 days apparently clear.

4. 43 out of 45 cases of ecthyma were discharged cured in an average of 12.3 days.

5. Boils do not respond to local penicillin but may do well with parenteral treatment.

PENICILLIN IN VENEREAL DISEASES

By Lt.-Col. D. J. Campbell, RAMC, Adviser in Venereology, 21 Army Group

The campaign in NW Europe, commencing as it did towards the end of the fifth year of the war, called in particular for methods which would save the greatest amount of manpower. Where medical aspects were involved, this saving of manpower had to combine the highest permanent cure rate as well. In all wars venereal disease had taken a heavy toll of the armies' strength, with long hospitalisation or absence from duty during post-hospital treatment. The advent of the sulphonamide drugs considerably reduced the loss in gonorrhœa in the early years of this war, but the gradual falling off in their effectiveness, amounting to almost complete failure in the Mediterranean campaigns of N. Africa, Sicily, and Italy, had thrown us back to the depressing conditions of the past.

The advent of penicillin and its effectiveness in both gonorrhœa and syphilis considerably reduced the problems, and tended towards complacency as far as venereal diseases were concerned. As with all new treatments the early results were strikingly successful. Gradually it has become apparent that to diagnose the condition and apply penicillin are not the only requirements, for apparent and actual failures do occur.

Considerable variations in the results obtained by different workers have been difficult to explain, especially as the sources of disease and the penicillin available have been common to all. It is not intended to detail the methods of preparation of penicillin in this article as the standards have been fully explained elsewhere, but the greatest stress is laid on the need to maintain the highest standards of technique especially as regards sterility and regularity of application. Many failures have resulted from carelessness or neglect of fundamental principles. The results quoted are those of British Army Venereologists in the main.

In a campaign of great movement it has not been possible to do as many laboratory investigations, such as blood level estimations, etc., as would have complemented the clinical and bacteriological assessments of cases, but where it has been possible to carry these out, no parallel between blood level of penicillin and clinical response has been manifest.

SYPHILIS

In this series all the cases were early, with chancres, local or generalised adenopathy, and few with more than mild skin and mucous membrane manifestations, for the soldier has been educated to report early signs. Only cases which have been under surveillance up to six months are reviewed.

Treatment was carried out in General Hospitals or VD Treatment Centres attached to FDSs or other forward medical units. Practically no patients required to be confined to bed, although some clinicians preferred to treat them in bed for the first 24 hours.

The dosage was 2,400,000 Oxford Units given in 40,000 unit doses, intra-muscularly, every three hours for seven-and-a-half days. Although various sites were used, the average patient tolerated, and even preferred, all injections in the upper and outer gluteal quadrants alternately. Local pain was rare and no abscesses resulted.

In up to 30% of cases a mild generalised reaction occurred, usually within the first 24 hours, with rise of temperature to 100-101°F, some with the appearance of mild rashes, while those with secondary rashes already present showed increased manifestations. This form of reaction has not been found in gonorrhœa or other conditions, and is in the nature of an Herxheimer reaction.

A few cases developed a temperature of 104°F, some showed urticarial response, one with involvement of multiple joints, but all continued the treatment in full, injections of adrenaline being used in the worst urticarial types.

Many cases Kahn negative at first gave a positive reaction after treatment. Chancres did not heal any quicker than with neoarsphenamine, and the average stay in hospital was 10 to 11 days. Considerable time and transport was subsequently saved in that, instead of the weekly attendance for injections of arsenical drugs, the patient is only reviewed at 2, 4, 6, 9, 12, 18 and 24 months.

It is worthy of note that 6 cases developed jaundice within 100 days after treatment at one centre, and one from another centre. This may have been sheer coincidence, but a number of gonorrhœa cases treated at the same time also developed jaundice. As the penicillin and solvent were drawn from a source supplying many units and no similar results have been notified, the question of syringe infection cannot be ruled out.

The results appear good, but lengthy surveillance must be carried out in all instances.

Three cases of reinfection within three months of previous penicillin treatment for syphilis were met. As the average patient re-exposed to infection is loath to admit it, the fact should be remembered; many cases quoted as relapses by other writers may well be re-infections.

The number of cases reviewed in the following tables is not great, but surveillance of treated cases has been difficult with the battles terminating the war in Europe. If arsenic and bismuth had remained the mode of treatment serious default must have resulted from the same cause. The figures quoted appear to be generally representative of the results in BLA. The bogey of suppressing or aborting syphilis acquired at the same time as gonorrhœa by using penicillin does not seem a big one, if treatment is kept to less than 250,000 units. Even then the chancre tends to have a longer incubation—often 10 weeks—is less typical, especially in respect of induration, and often sparse in Spirochaetes. All gonorrhœa cases should have surveillance up to 6 months to assure that syphilis has not been missed.

EARLY SYPHILIS

(1)	*Sero-Negative* at time of diagnosis and remaining so at subsequent surveillance to 6 months	143	(48.3%)
	Of these 12 (8.4%) showed a positive Kahn after treatment, but had reverted at 2 months. A much higher percentage probably gave this result, but it was not routine in all centres to repeat the Kahn before the 2 months surveillance.		
(2)	*Sero-Negative becoming Sero-Positive* ...	6	(2.03%)
	5 became positive at 2 months. 1 became positive at 4 months. All remained positive at 6 months but were less than 20 Kahn units.		
(3)	*Sero-Positive becoming Sero-Negative* ...	140	(47.3%)
	48 became negative at 2 months. 72 became negative at 4 months. 20 became negative at 6 months.		
(4)	*Sero-Positive remaining Sero-Positive at 6 months*	7	(2.36%)
		296	

GONORRHŒA

The cases reviewed in this series fall into two groups:

(*a*) Those which had failed to respond to sulphonamides.

(*b*) Those without previous treatment.

It was soon evident that penicillin, in aqueous solution, should be given three-hourly in doses of 15,000 to 20,000 units to a total of 100,000 to 120,000 units.

The course of the disease is variable. At 24 hours there is usually a urethral discharge showing a large amount of pus, but no gonococci. In some instances gonococci are still present but are swollen in appearance and do not grow readily, if at all, on culture media. The urethral discharge usually persists up to 7 to 10 days, a fact which at the beginning caused many venereologists to continue treatment with adjuvant methods such as irrigations, alkalis, or even sulphonamides. As experience increased it was realised that if he was co-operative, drank plenty of water and avoided alcohol, the patient could return to his unit with a high expectancy of cure in a few days. This again proved to be an immense saving of manpower and hospital beds.

(1) SULPHA RESISTANT ... ... Total 1602
These cases still showed gonococci after 4 days treatment with 5gms. sulphonamide (mostly sulphathiazole) daily, a total of 20gms.

(*a*) *Non-Complicated.*
(i) Cured with 1 course of penicillin.

	No. of cases	No. requiring adjuvant treatment	%
3 injections of 50,000 units	13	3	23
6 injections of 15,000 units plus one of 10,000 units	208	4	2
5 injections of 20,000 units	300	8	2.7
8 injections of 15,000 units	788	40	5.1
6 injections of 20,000 units	188	33	17.5
Totals	1497	88	5.9%

Adjuvant treatment was given where discharge continued to be profuse but gonococci were absent. The high percentage in the 6 injections of 20,000 units course was due to temerity on the part of the venereologist as compared with the one using the 5 injection course.

(ii) Failed with 1 course of penicillin (*i.e.* still gonococci positive) ... ... 26 = 1.7%

Most of these responded to a second course averaging 150,000 units, but three required a further course. In none were the organisms proved penicillin resistant in vitro.

(*b*) *Complicated.*

(i) Cured with one course of penicillin.

Arthritis	3
Epididymitis	30
Prostatitis and Vesiculitis	13
Littritis	19
Total:	65

In all these cases the suitable adjuvant treatment was given as well.

(ii) Failed with 1 course of penicillin (*i.e.* gonococci positive).

Arthritis	3
Epididymitis	5
Prostatitis and Vesiculitis	2
Littritis	4
Total:	14

(2) GONORRHŒA FRESH AND UNTREATED

(*a*) *Uncomplicated.*

(i) Cured with one course—injections at three-hourly intervals.

	Cases.	No. requiring adjuvant treatment.	%
6 injections of 15,000 units plus 1 of 10,000 units	196.	Nil.	
5 injections of 20,000 units	215.	5.	2.32
8 injections of 15,000 units	491.	20.	4.07
6 injections of 20,000 units	192.	13.	6.7
1 injection of 40,000 units plus 5 of 20,000 units	86.	Nil.	
Totals.	1180.	38.	3.2%

It seems that the course giving 40,000 units as a first injection followed by five of 20,000 three-hourly considerably reduces the number of days during which the discharge persists.

(ii) Failed on one of the abovementioned courses ... 11
(iii) Failed on two of the abovementioned courses ... 3

(*b*) *Complicated.*

(i) Cured on one of the abovementioned courses with customary adjuvant treatment for the complication.
Epididymitis 10
Arthritis 1

(ii) Failed on one of the abovementioned courses.
Epididymitis 4
Arthritis 5

(*c*) *Complications after apparent cure.*
Epididymitis at 3 weeks 2
Epididymitis at 4 weeks 1
Arthritis at 4 weeks 2

It is of interest that these cases did not show a relapse of the original urethritis.

(3) Cases Treated on Rapid Courses

In an endeavour to further reduce the man-hours lost several rapid course of therapy were tried.

(i) 8 *injections of* 12,500 *units at* 15 *minute intervals.*

If there was not bacteriological cure in 24 hours the course was repeated.

Cured on one course	93 = 57%
Cured on two courses	45 ≐ 27.6%
Cured on three courses	7 ≐ 4.2%
Failed on three courses but cured with a further routine three-hourly course	19 = 11.5%

(ii) *Cases treated with penicillin in slow release vehicle*
Total 400
Calcium penicillin was injected in 3ccs of 3% Cera Flav. in Ol. Arachis.
Each series consisted of 100 cases.

Method.	% cure.	How treated.
1st Series.		
100,000 units calcium penicillin in one injection	77	Hospitalised 8 days.
2nd Series.		
As in 1st Series with additional 40,000 units sodium penicillin. Both injections given at same time	94	Hospitalised 8 days, but with heavy fatigues.

3rd Series.

As in 2nd Series ...	88	Treated as out-patient and reviewed at 4 and 8 days after full duties.

4th Series.

Ca. penicillin 150,000 units in slow release vehicle	95.8	Treated as out-patient on full duties.

This group of cases has not been followed to full tests of cure, but, to date, has shown no relapse after initial cure.

NON-GONOCOCCAL URETHRITIS

Total ... ... 150 cases

1. NON-COMPLICATED

	Cases.	Required adjuvant treatment
(*a*) Cured with one course of penicillin (three-hourly injections) after failure with sulphonamides	86	14
(*b*) Cured with penicillin alone... ...	24	9
(*c*) Failed with sulphonamides plus one course penicillin (without adjuvant treatment)	21	—

2. COMPLICATED

Failed with sulphonamide plus one course penicillin (without adjuvant treatment).

Epididymitis	14
Littritis	4
Prostatitis	1

This series of 150 cases shows the relative failure of penicillin as compared with results in gonococcal urethritis.

SUMMARY

SYPHILIS

The use of penicillin in the treatment of early syphilis shows a relatively high percentage of success, and the 4-5% failure must compare very favourably with the failures which resulted through the default during treatment under the long-term arsenic and bismuth treatments. In two campaigns of considerable movement—Mediterranean and N.W. Europe—it is our opinion that this default amounted to 50% of cases.

Even in civil practice where default of treatment is one of the greatest difficulties, penicillin treatment would appear the method of choice, except that the average civilian could not afford to be hospitalised for at least eight days.

Gonorrhœa

The three-hourly administration of penicillin has shown a high percentage of success, but the promise of one or two injections with a slow release vehicle is great with 95% cure results.

Non-Specific Urethritis

In this condition penicillin has not proved to be anything like as efficacious as compared with its results in gonorrhœa.

From the military point of view, penicillin has materially saved manpower, hospital beds and transport. Whilst 100% cure has not been attained, especially in syphilis, the risk of relapse is very much less than under prolonged arsenic and bismuth with a high default rate.

Provided social conditions will allow, penicillin will have considerable influence in civilian treatment.

GONORRHOEA TREATED BY PENICILLIN IN A SLOW RELEASE VEHICLE

By Major R. F. M. Child, RAMC, Specialist Venereologist, Major K. E. A. Hughes, RAMC, late Officer i/c No. 3 Mob. Bact. Lab., and Major R. W. Evans, RAMC, Officer i/c No. 3 Mob Bact. Lab.

TYPE OF CASE TREATED

Consecutive unselected cases of acute gonorrhoea reporting for treatment in the Outpatient's Department of the Special Wing, 111 (Br) General Hospital, BLA. They are grouped in series of one hundred cases and this report deals with 400 cases.

The majority had had no treatment previously, but some were relapses or failures following chemo-therapy.

THERAPEUTIC AGENT

Calcium penicillin (100,000 units per 3 cc.) in 3% Cera Flav. in Ol. Arachis.

METHOD

(*a*) One intra-gluteal injection of Ca. penicillin in the slow release vehicle. This was given in the evening of the day of diagnosis and no further treatment of any kind was given subsequently.

(*b*) Owing to the extreme viscosity of the vehicle at room temperature transfusion needles are used, and the vehicle is warmed (to body heat) for three minutes, and well shaken, just prior to injection.

(*c*) Heavy fatigues (stretcher bearing, etc.) were undertaken during the period of observation in the first two series. The subsequent series were treated as outpatients and carried on with normal duties all the time.

(*d*) Relapses received Sodium penicillin in six 3-hourly intramuscular injections on the same day that relapse became evident on examination of the early morning smear; each injection contained 20,000 units in aqueous solution—total dosage 120,000 units. The cases were observed for one week after injection. Early morning

smears were examined daily. During their period of observation heavy fatigues, including stretcher bearing, were undertaken without apparent ill effect.

RESULTS

Series of 100 cases	Method	Percentage Clinical cures	Average time for Urethral Discharge to dry	Hospitalisation
1st series	Ca. Penicillin 100,000 units in Slow Release Vehicle (one injection).	77%	4.75 days	Yes 8 days
2nd series	Ca. Penicillin 100,000 units in Slow Release Vehicle. Na. Penicillin 40,000 units (aqueous). (Both injections given at same time.)	94%	4.13 days	Yes 8 days (Heavy fatigues
3rd series	As 2nd series (Outpatient surveillance at 4th and 8th day).	88%	—	No. Full duties
4th series	Ca. Penicillin 150,000 units in Slow Release Vehicle (one injection).	96%	—	No. Full duties

SUMMARY OF CLINICAL RESULTS

(*a*) The results of treating acute gonorrhoea by one injection of Ca. penicillin in a slow release vehicle are given.

(*b*) The fourth series employing a larger dose of penicillin promises to be the best of the methods to date.

(*c*) The probability that acute gonorrhoea will be curable by one intramuscular injection, without interference with normal duties, is visualised.

THE USE OF SLOW RELEASE VEHICLES IN PENICILLIN THERAPY

Owing to the rapidity with which penicillin is excreted by the kidneys, one of the greatest difficulties in its use is the maintenance of an adequate bacteriostatic level in the blood. Various methods have been suggested to overcome this, such as the concurrent administration of diodrast or p:amino-hippuric acid to delay excretion. Another way is to use some vehicle to slow down the rate of absorption of penicillin into the circulation after its injection.

Several methods have been tried out in the past six months.

1. Oil in Water Emulsions: A 50% emulsion of Ol. Arachis in water was made, using gum acacia as the emulsifacient.

Sodium penicillin in solution was added to this so that the final mixture contained 150,000 units in 3 ccs. of the emulsion, which then contained 37.5% oil; 3 cc. doses of this were injected intramuscularly into each of two patients. No complaint of pain was made.

A bacteriostatic blood level was maintained in one patient for 4 hours and in the second for only two hours. As this was no better than could be expected from a simple aqueous solution of the same strength the method was abandoned. As a matter of interest, the first of these patients was suffering from acute untreated gonorrhœa. He was cured, the discharge ceasing in 48 hours. He did not relapse.

2. Water in Oil Emulsions: Using Cera flavum as the emulsifacient, an emulsion was made containing about 92% Ol. Arachis. Sodium penicillin was dissolved in the water to give a final concentration of 200,000 units in 3 ccs. of emulsion.

Two cases of acute gonorrhoea were given 3 ccs. each intramuscularly. Again there was no complaint of pain. One maintained a bacteriostatic blood level for about 3 hours and the other for 5 to 6 hours. Both were clinically cured.

3. Suspensions in Oil and Wax: Following the work of Romansky and Rittman it was next decided to try a suspension of calcium penicillin in Ol. Arachis and beeswax.

Cera flavum was melted in a water bath and filtered through six layers of gauze while still hot, a clear fluid resulting. Using a warm pipette, 3 ccs. was added to 97 ccs. of warm Ol. Arachis and mixed. The mixture was placed in a screw-capped glass bottle, sterilised in the autoclave at 20lbs for 20 minutes, and then kept in the water bath at about 50-55°C. An ampoule containing 100,000 units of calcium penicillin (Commercial Solvents Corporation) was vigorously shaken by hand until the powder was as finely divided as possible.

3 ccs. of the hot oil-wax mixture was put into a warmed 25 cc. sterile screw-capped glass bottle with a warm sterile pipette and the contents of the ampoule added after flaming the mouth. Six glass beads were also put in and the bottle was shaken vigorously by hand to suspend the penicillin. It was found that one of these bottles would conveniently hold 21 ccs. of oil-wax mixture, the contents of seven ampoules of penicillin and the half dozen beads, and that vigorous shaking by hand for about 5 minutes resulted in a reasonably fine and even suspension of penicillin. On cooling to room temperature the mixture is rather thick and difficult to handle so it should be warmed in a water-bath at 37°C or an incubator for a few minutes before use, when it can be again shaken vigorously to re-suspend the penicillin.

10 cc. Record syringes which should be warm are filled from the plunger end, before the plunger is put in. A serum needle can be used to make the injection, but a blood transfusion needle makes it easier. The needle is inserted intramuscularly into the gluteals before attaching the syringe as in giving Bismuth injections.

In the first 18 cases treated estimations of the bacteriostatic levels in the blood were made every hour for 7 hours. The results are shown in the table, together with the results of six 100,000 unit injections in saline for comparison. Examinations of the urines were made simultaneously and again at 24 hours. Penicillin was present in all specimens of urine in bacteriostatic amounts.

TABLE I

Case No.	Oil-Wax mixture. Dilution of patient's serum showing complete bacteriostasis. Time interval in hours after injection.						
	1	2	3	4	5	6	7
1	1/4	1/8	1/4	1/2	1/1	1/2	0
2	1/4	1/4	1/4	1/2	0	0	0
3	1/8	1/4	1/4	1/2	1/1	0	0
4	1/4	1/4	1/2	1/1	1/1	0	0
5	1/8	1/8	1/8	1/4	1/4	1/1	1/1
6	1/8	1/8	1/8	1/4	1/8	1/2	0
7	1/4	1/8	1/8	1/8	1/2	1/2	1/1
8	1/8	1/8	1/4	1/4	1/1	1/2	1/2
9	1/2	1/2	1/4	1/2	1/1	1/1	1/1
10	1/8	1/8	1/4	1/2	1/1	1/1	1/1
11	1/8	1/8	1/4	1/4	1/2	1/2	1/1
12	1/8	1/4	1/4	1/2	1/1	1/1	1/1
13	1/8	1/4	1/4	1/2	1/1	1/1	1/1
14	1/4	1/4	1/2	1/1	0	1/1	1/1
15	1/8	1/4	1/4	1/2	1/1	1/1	0
16	1/8	1/8	1/4	1/1	1/1	0	0
17	1/2	1/2	1/4	1/2	1/1	1/1	1/1
18	1/4	1/4	1/2	1/1	1/1	0	0

Saline solution

1	1/64	1/16	1/2	1/1	0	0	0
2	1/128	1/16	1/4	1/1	0	0	0
3	1/32	1/4	1/1	0	0	0	0
4	1/16	1/8	1/1	0	0	0	0
5	1/16	1/2	0	0	0	0	0
6	1/16	1/8	1/2	0	0	0	0

Serum penicillin levels were also determined at varying time intervals after injection in 27 further patients. Estimations of bacteriostasis were carried out hourly to cover a period of 8 to 26 hours after treatment (Table II—See next page).

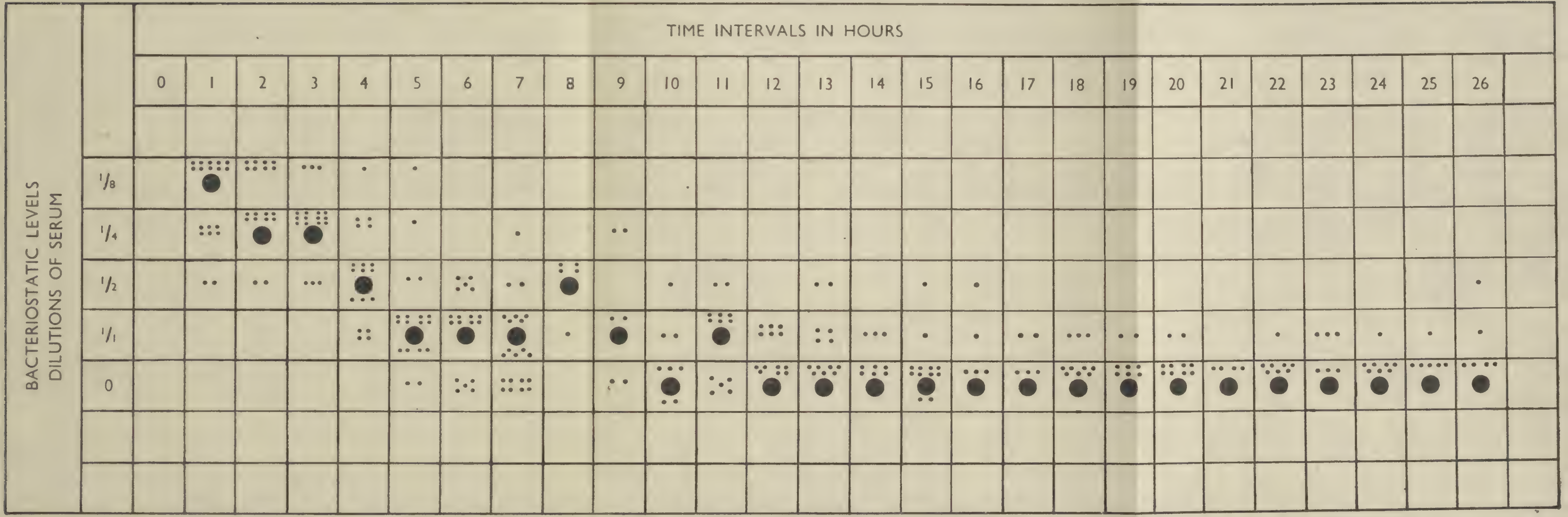
TABLE II

TABLE II SHOWING VARIATION IN BACTERIOSTATIC LEVELS IN CORRELATION WITH DURATION OF TIME AFTER INJECTION IN HOURS

Bacteriostatic levels. Dilutions of serum.	Time interval in hours.																								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26
1/8	10	8	3	1	1			1																		
1/4	6	8	12	4	1		1		2																	
1/2	2	2	3	9	2	5	2	4		1	2		2		1	1										1
1/1				4	12	8	10	1	2	2	6	6	4	3	1	1	2	3	2	2		1	3	1	1	1
0					2	5	8		2	5	5	7	7	6	10	3	3	7	6	8	4	7	3	7	5	4
Total cases examined	18	18	18	18	18	18	21	6	6	8	13	13	13	9	12	5	5	10	8	10	4	8	6	8	6	6
Modes	1/8	1/4	1/4	1/2	1/1	1/1	1/1	1/2	1/1	0	1/1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

TABLE III.

SCATTER DIAGRAM SHOWING DISPERSION OF RESULTS ABOUT THE MODES.



From the tables it will be seen that absorption is not absolutely regular and that in over half the cases bacteriostasis was prolonged to at least 9 hours whereas with the saline solution in only 2 cases was the period of 3 hours exceeded. In a few instances irregular blood levels were obtained even at 24 hours after the exhibition of penicillin suspension.

TABLE III (*see folded page*)

Table III shows the dispersion of the results about the "crude" modes obtained in the investigation. The mode is the measure representing the vogue of the series, viz, the most frequent and therefore probable value. It possesses the advantage of being independent of abnormal values or events.

WEIL'S DISEASE

By Brigadier E. Bulmer, Consulting Physician, 21 Army Group

Sporadic cases of Weil's disease have occurred in 21 Army Group, and the opportunity has been seized of treating them with penicillin.

HISTORY OF OUTBREAK

Weil's disease is spread by infected rats who pass the leptospiræ in their urine. The organisms can live for some time in stagnant streams, wells, and in the zooglea-like substance on the walls of wells and sewers. The source of the infection was almost certainly water which men used for washing. Drinking water was supplied from water carts or sterilised in some other way, but the supply was not sufficient for other uses. They were forced to draw water from wells or streams for washing, shaving and brushing their teeth. They bathed when they could in any available stream. On some sectors they lived in damp, rat-infested ditches.

Up to date (December, 1944) cases have only been met with in Normandy, and only during the period from the middle of July to the end of September. It is surprising that conditions in the Low Countries have not produced further infections.

I saw the first case recognised on 18 July, 1944, with Maj. C. L. Davidson in a CCS near Caen. The patient had had a febrile illness with severe muscle pains and a leucocytosis. On the tenth day he had a very faint icteric tint in his conjunctivæ but was convalescent. We discussed the possibility of Weil's disease, and a few days later we learnt that the agglutination test was positive.

Cases cropped up in many units, and when the outbreak ceased at the end of September I had been informed of 39.

It is difficult to compute the extent of the outbreak. My figures must be incomplete, and cases must have been missed, especially those without jaundice. Of the 39 cases only two did not have jaundice, whereas they should have equalled those with jaundice. I would make an informed guess that about 100 cases occurred altogether.

Some cases were very severe, and supplies of anti-leptospiral serum at first were scanty. The leptospira is moderately sensitive to penicillin, and it was decided to use it in treatment.

In only one case—the only fatality in the penicillin series—was anti-leptospiral serum given.

CLINICAL FEATURES

These are well dealt with in the standard text-books, but those of us who were little familiar with the disease were struck by its unusual features: a brisk febrile illness with severe muscle pain as the leading symptom, associated with a leucocytosis and complicated by signs of gross renal damage. In the presence of an outbreak this picture is highly suggestive even if jaundice does not follow.

In all but two of the cases jaundice developed on or after the fifth day. In sharp contrast to "infective hepatitis" the temperature did not subside when jaundice appeared. It usually increased, and the urine still showed the signs of renal damage. In most cases there was some hæmorrhagic incident—conjunctival ecchymosis, epistaxis, hæmoptysis, hæmatemesis, purpura.

The disease if at all severe ran a longish course, and the temperature was maintained for perhaps two weeks. There were often febrile relapses later and patients were very debilitated.

Of the special types described the anginal form was rare. There were three examples of the meningeal form, but only one had an abnormal cerebrospinal fluid. Lung involvement with hæmoptysis, water sputum, and abnormal signs, both physical and radiological, was not uncommon.

LABORATORY FINDINGS

Leptospirae were found in the blood in several cases, and in the urine in quite a number—both by darkground illumination. Animal inoculation was rarely possible. In most of the cases positive agglutination tests were obtained by sending blood to the UK.

RESULTS

1. Total cases 39
2. **Penicillin treated** 16
   8 severe, 7 moderate, 1 mild (14 confirmed by agglutination tests; 1 died of uræmia)
3. **Untreated** 23
   2 died (one of myocarditis on 21st day, one of uræmia soon after admission)

PENICILLIN TREATMENT

The dosage recommended was 40,000 units three-hourly, with a total of about a million units. The average amount given was 1,125,000 units; some was by continuous intramuscular drip, some by intramuscular injection, and there was some variation in dosage.

Our difficulties in assessing the results have been great. The disease rapidly inflicts severe damage on liver and kidneys, and any treatment to be successful must be given early enough to

anticipate this, perhaps at a time when a diagnosis is impossible to make. No case was treated in the pre-icteric stage when there was the best chance of rapid resolution. Even if penicillin should prove to be a specific remedy, it seems doubtful how often really early treatment will be practicable, unless in the presence of so big an epidemic that everyone becomes very skilled in early diagnosis.

We have been unable to find any satisfactory measurement of progress, except the effect of the drug on the temperature and on the number of febrile relapses, and we were left with a clinical impression.

Most of the severe cases received penicillin and recovered. All observers claimed a dramatic improvement in 36 hours, which was usually reflected in the temperature chart, but with slow improvement in jaundice and urine. In the fatal cases I doubt whether any treatment would have saved the two who died of suppression of urine (one treated and one not treated); the third case was not thought severe enough to need penicillin, and he died of auricular flutter on the 21st day. This should have been averted if there had been a specific treatment.

Lt.-Col. L. H. Howells and Maj. R. R. Hughes made an intensive study of seven cases, six of whom they treated with penicillin. Their conclusions were as follows:—

1. Penicillin in adequate doses appeared to shorten the general effects of the disease as assessed by the duration of the fever. It had an effect on the number of febrile relapses, and these effects bore a direct relationship to the dosage.

2. Penicillin did not appear to influence the degree and duration of the cholæmia as estimated by the icteric index and the Van den Bergh test, or to affect the rate of disappearance of icterus from the skin or bile from the urine.

3. Penicillin did not influence the degree of nitrogen retention as estimated by the blood urea, or the degree or rate of disappearance of albuminuria.

4. Apart from the objective evidence mentioned in para 1 there only remains the very definite clinical impression that cases treated with penicillin, especially with high doses, improved dramatically within 36 hours.

5. It is considered that penicillin should be given in cases of Weil's disease as soon as possible and in high doses. Once liver and kidney damage have occurred penicillin does not appear to minimise the results of these, hence it would be interesting to observe the effects of the drug during the pre-icteric phase.

CONCLUSION

Penicillin is apparently of benefit in Weil's disease, but really early treatment will seldom be possible—unless during an epidemic when everyone has the disease in mind and becomes skilled in early diagnosis.

REACTIONS AND COMPLICATIONS IN PENICILLIN THERAPY

By Lt.-Col. G. A. G. Mitchell, RAMC, Adviser in Penicillin and Chemotherapy, 21 Army Group

Penicillin is the nearest approach to the ideal antiseptic yet discovered. It is non-toxic; it inhibits or destroys a wide range of pathogenic organisms; its activity is almost unimpaired in the presence of serum, pus and tissues autolysates; its action is largely independent of the number of organisms present; it does not interfere with the normal defence mechanisms; and in pure form it is unirritating to the most delicate tissues. Our experience in 21 Army Group supports all these claims, and while reactions and complications have occurred following the use of penicillin, considering the total numbers involved they have been very uncommon. At a conservative estimate between 90,000 and 100,000 men have had penicillin treatment in this theatre since "D" Day, and at least one-third have received it by the parenteral route.

TOXIC EFFECTS

No poisonous effects have been encountered.

SENSITIVITY

There have been two severe cases. In both the responsibility of penicillin for the reaction seems reasonably well established. One of these is reported separately by Michie and Bailie. The other was a case of exfoliative dermatitis that occurred during treatment of a man with syphilis.

There have been a considerable number of cases of urticaria or dermatitis where penicillin came under suspicion, but as sulphonamides had also been used in practically every case no one was prepared to apportion the blame. In several patients patch tests revealed some degree of penicillin sensitivity, suggestive but not conclusive evidence that penicillin was the cause, especially as some also reacted to sulphonamide, and one to lanette wax (this particular patient had been treated with penicillin cream). There can be little doubt, however, that penicillin skin reactions of this type do occur, although one cannot put a definite figure on the number that have occurred

in this theatre. But one can say this. With the exception of those mentioned at the beginning of this paragraph none have been severe.

PYREXIA

Three pyrogenic reactions have been reported, all following intramuscular administration (two continuous drips and one by intermittent injection). All had malaise and temperatures up to 103-104°F. None had rigors. One later developed a coliform abscess at the site of the drip, and in the two others it was discovered that the saline used as solvent was contaminated with moulds. The evidence that penicillin was responsible was slender, particularly as scores of other patients had been treated with the same batches with no untoward results.

Four men developed temperatures ranging up to 101-102°F. following injection of one particular batch, but the most prominent feature was pain, even although the penicillin was well diluted (100,000 units in 540 ccs. normal saline) and administered by intramuscular drip. This batch was not used further and was returned to the UK for examination. The results are unknown.

Many officers have noted a somewhat different effect—a mild and persistent pyrexia during the course of continuous intramuscular administration. The temperature may have been elevated initially to 101-102°F, due to the infective process. The infection subsides following penicillin treatment and the temperature settles to just above normal, usually between 99-100°F. It persists at this level as long as penicillin is being given and returns to normal within 24 hours of the cessation of treatment. This has now happened so often that the possibility of coincidence can be eliminated, and it is presumed that on these occasions either the penicillin or the solvent contain pyrogenic elements.

PAIN

The pain resulting from the actual injection varies from case to case, and depends on various factors such as the amount of fluid used and the rate of injection, the sensitivity of the patient and of the part selected, and the brand and dosage of penicillin employed. Small doses injected slowly into the outer side of the buttock or thigh, using a sharp needle, produce only mild discomfort in the majority of cases. When large doses are given (100,000 units in 2-3 ccs. distilled water) more pain is produced, especially if the injection is given subcutaneously rather than intramuscularly.

Some batches of penicillin definitely cause more pain than others, and it is significant that the less concentrated varieties—as judged by larger bulk and darker colour in powders or the

lower penicillin content in tablets—are most liable to produce pain. This suggests that associated impurities rather than penicillin itself are the main source of the trouble. Certain batches giving off an inflammable vapour are particularly liable to produce pain.

Many patients evince an increasing aversion towards repeated "needling", and object particularly to being awakened once or twice for injections during the night. Some do not distinguish between the pain produced by the actual skin puncture and the injection. Others definitely do, and state that the fluid causes burning and smarting which persists for anything from 3-30 minutes. When treament is only required for several days—and this includes the majority of cases—the patients seldom raise serious objections to the repeated injections, but if they have to be continued for a longer period "needle shyness" may become a real problem. Pain and "needle shyness" are much less evident when continuous administration is properly employed, and this method is frequently used in this theatre in treating men likely to require penicillin for more than 3-4 days. Indeed many surgeons regard this as the method of choice for all cases. Venereal cases are excluded from this generalisation; for various reasons they tolerate injections relatively well, and they are usually ambulant during treatment.

Procaine or percaine are occasionally used, and are effective as the following episode reveals*:—In December, 1944, 12 Canadian General Hospital was using a batch of penicillin that produced much more pain than usual. The bacteriologist there prepares all penicillin solutions for use in the wards, and because of the frequent complaints of pain he began adding procaine as a routine to the solutions. As soon as he adopted this procedure the complaints practically ceased. One day, without informing anyone, he deliberately omitted the anæsthetic agent in the solution supplied to one ward. The nurses reported immediately that the patients in this ward were all complaining, whereas no moans were received from the other wards.

IRRITATION

Irritation and pain are inter-related, and both appear to be due mainly to impurities. Undiluted penicillin of any type presently supplied produces a stinging sensation when applied to a wound, but the irritant effect is largely abolished when the penicillin is diluted down with sulphonamide or when dissolved in isotonic saline to give a concentration of not more than 5000 units per gm. or cc. Even then, however, certain of the less pure brands still cause pain, but some of the best brands now

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* See also "Local Anaesthetics and Penicillin Therapy" by Major F. F. Rundle.

available produce no pain even in much higher concentrations.

Apart from the pain, more serious effects may follow the injection into serous or synovial spaces of impure penicillin, or the excessive or over-prolonged use of any preparation. Inflammatory changes occur, fibrinous masses may form in the effusions, any contained blood may clot, and the membranes may become thickened. In the case of meningitis the cell count in the CSF may remain abnormally high after the infection has been overcome, due to the irritation produced by impurities in the penicillin.

These irritative effects in body cavities are now so well appreciated by most physicians and surgeons that they use only the purest brands of penicillin available, and are careful to avoid excessive or over-prolonged use.

In two patients shock and collapse occurred following intrapleural instillation of impure preparations, and a similar occurrence has been reported once following an ordinary intramuscular injection. Fortunately the men responded rapidly to resuscitative measures, and did not show similar effects when treated subsequently with another and better brand of penicillin.

THROMBOSIS AND PHLEBITIS

During June and July, 1944, penicillin was often given by the intravenous route, either by repeated injections or in saline or saline-glucose drips. This method was soon abandoned as thrombosis frequently occurred and aroused the ire of anæsthetists and others. It was unusual for a drip to run for more than 30 hours and many blocked hours earlier, especially when saline-glucose was used as the vehicle. In a few cases done in Canadian CCSs, where heparin was being used coincidently following arterial suture, the clotting was abolished or delayed, but heparin was very difficult to obtain and in any case its widespread use without careful control would have been unwise.

Any associated phlebitis was usually mild, but in one case it was severe. This occurrence, plus the high incidence of thrombosis in other cases, led us to discourage administration by the intravenous route.

During the period January-March, 1945, Lt.-Col. Heatley, Lt.-Col. Young and Maj. Hughes, while investigating the results of intensive therapy, often administered penicillin intravenously, usually injecting 15,000 units every 15 minutes for 1½-2 hours through the tube of an isotonic saline drip. The results of some of these experiments are reported elsewhere in this brochure. They are merely mentioned here because it was found that thrombosis was not produced with the purer brands of penicillin now available.

STIFFNESS

This is most common following continuous intramuscular administration into the vastus lateralis, and may be associated

with mild induration. It is normally slight and transient if certain details in technique are observed—the fluid is not allowed to run in too rapidly, the site is changed every second day, the needle is inserted parallel to and not across the line of the fibres and is fixed securely to prevent wobble, and the patient is warned to avoid sudden or excessive movements of the limb during the administration.

INFECTIVE COMPLICATIONS

These have been rare. There may have been a few undiscovered cases and others may have developed after evacuation from this theatre, but it is believed the following figures are very near the truth:—

12 abscesses;
6 sterile collections of fluid;
3 cases of cellulitis;
1 doubtful abscess.

All the abscesses followed intramuscular drips. Seven were due to coliform organisms, one to Ps.pyocyaneus, and in four the bacteriology could not be discovered owing to the absence of laboratory facilities near the units concerned. None was severe, and the infection subsided rapidly following incision and drainage.

The six sterile abscesses also followed drip administration and apart from some stiffness they too caused no subsequent trouble.

The doubtful abscess occurred in a case following intermittent injections into a buttock. A nurse reported after the man was evacuated that she had noted a painful and indurated mass at the site of the injections; presumably he was developing an abscess.

All the cellulitis cases involved the thigh; two followed intramuscular drips, and the third followed repeated injections. The local and general reactions were severe, but none broke down or required incision and so the actual pathogens were not determined.

Considering the conditions under which many intermittent and continuous injections had to be given, and that the total number must amount to several hundred thousands, the incidence of infection has been surprisingly low. It has been much lower than was anticipated, and in the earlier days various experiments were carried out by adding low dilutions of various substances such as sulphadiazine, sulphamezathine, and p-benzylamine-sulphonamide to the saline in the hope that infection with penicillin-insensitive organisms would thereby be avoided. Potassium tellurite was to be tried also, but on the advice of Sir Alexander Fleming it was not used as he feared it might

prove toxic even in low dilutions, and we were uncertain about cumulative effects. Fortunately it soon became apparent that infection was not a problem and these experiments were then terminated.

SUMMARY

A number of reactions and complications following the use of penicillin in 21 Army Group have been described. The incidence of all has been extremely low considering the large number of patients treated.

PENICILLIN REACTION: REPORT OF A CASE

By Major W. Michie, RAMC, Surgical Specialist, and Capt. H. W. C. Bailie, RAMC, Rususcitation Officer

Compared with the sulphonamides penicillin has maintained a relatively unclouded reputation as regards reactions and complications. The following case is therefore of interest.

On 7 September, 1944, a tank officer was wounded by a small shell fragment which became embedded in his right calf. This was removed an hour later and a sulphanilamide dressing applied. The officer remained on duty, but on 19th September the leg became painful and swollen. He was admitted to a field dressing station where sodium sulphate dressings were applied. On 24 September sodium penicillin solution was instilled directly into the wound and this was repeated the following day. On the 2 October he was admitted to a CCS where a sinus one inch long was opened up. Since this officer was a key man urgently required by his unit, undiluted penicillin powder without sulphonamide vehicle was applied (a much higher concentration than is normally employed) in the hope that recovery might be hastened. A similar application was made on 5 October. Progress was satisfactory and by the 10 October the wound had healed almost completely. On 11 October the patient intimated he had a mild chronic bilateral external otitis. At 17.00 hours on the same day two drops of sodium penicillin solution (100,000 units in 5 cc.) were instilled into each ear. By 02.00 the next morning both ears were discharging profusely. His leg, previously healed, began to weep copiously and literally saturated the dressings; and by evening, eczematous, weeping patches had broken out over both ears and the lower face and chin. On 13 October a penicillin patch test, consisting of two drops of penicillin solution on gauze, was applied to the intact skin of his arm. Within five hours the sensation was "similar to a TAB reaction" and the following morning the patch area exhibited a weeping eczema similar to the areas originally affected. A mild secondary infection of all areas subsequently developed; healing ensued gradually following treatment with "Nuflav" powder.

This patient was seen again in December. The leg remained soundly healed but the chronic otitis persisted.

The particulars of the penicillin used at the FDS are unknown. That used in the ear and leg at the CCS was Pfizer batch 1664, and for the patch test Pfizer batch 1594.

It is understood that this is the only occurrence of a reaction of this type to penicillin therapy in many thousands of cases treated in BLA.

It is impossible to tell whether it was due to penicillin itself or to associated impurities. Presumably, however, it was a matter of personal idiosyncrasy since many other cases were treated with the same batches of penicillin and exhibited no reactions of any kind.

OBSERVATIONS ON THE TREATMENT OF ACUTE ULCERATIVE GINGIVITIS BY PENICILLIN

By Major A. State, AD Corps, Specialist Dental Surgeon, and Major J. Hart-Mercer, RAMC, Specialist Pathologist

At the instigation of Brigadier E. Bulmer, OBE, Consulting Physician to 21 Army Group, it was decided to investigate further the therapeutic value of penicillin in acute ulcerative gingivitis; the ultimate aim being to ascertain the most effective and practical method of giving penicillin to Army personnel affected by this disease.

MATERIAL AND METHODS

All the cases covered by this report were admitted to 75 (Br) General Hospital and treated throughout as in-patients. No case was admitted unless he presented both the clinical features of acute ulcerative gingivitis and characteristic "Vincent's organisms" in smears from the gum pockets; otherwise no form of selection of cases was attempted.

Initially the patients were divided into three groups, and later into four when pastilles became available, according to the order of their admission to hospital.

The sodium salt of penicillin was used throughout.

Group I received 8 three-hourly intramuscular injections of 15,000 units each in the 24 hours (*i.e.* 120,000 units per diem).

Group II (a) had hourly mouth washes of one fluid ounce of 5000 units in sterile distilled water during waking hours (*i.e.* 15 times in the 24 hours, giving a dosage of 75,000 units per diem). Patients were told to retain the fluid in the mouth for at least five minutes.

Group II (b) (Mouthwash Control) had exactly the same treatment as Group II (a) except that the sterile distilled water contained no penicillin.

Group III were treated by an oral spray containing 100,000 units in 60 cc. sterile distilled water (except for the first 6 cases

in this group which received twice that strength) at the rate of 2cc. hourly for fifteen hours each day (*i.e.* 50,000 units per diem, except for the first six cases who had 100,000 units per diem). In an attempt to delay dispersion of the penicillin a strip of gauze was laid over the gums in these cases.

Group IV (a) received every 2 hours for 16 hours each day, gelatin pastilles containing approximately 500 units each (*i.e.* 4000 units per diem), the strength of gelatin being such that the pastilles took approximately two hours to dissolve in the saliva.
Group IV (b) were similarly treated, but received in addition "scaling" after clinical improvement was established.

Group IV (c), (Pastille control). The pastilles contained no penicillin but were administered in the same way for five days.

RESULTS

The clinical and bacteriological response to treatment in the several groups is summarised in the following table:—

RESULTS IN 138 CASES

Group	Mode of Administration of Penicillin	Daily Dosage	No. of Cases	Average time before clinical cure	Range	Average time before first of three successive negative smears	Range
I	Intramuscular	120,000 Units	20	3 days	1 to 4 days	7,6 days	1 to 17 days
II (a)	Mouthwash	75,000 Units	29	2.5 days	2 to 4 days	4.5 days	2 to 16 days
II (b)	Mouthwash Control	—	12	4 days	4 to 5 days	Bacteriologically positive after five days and treatment changed	
III	Oral Spray	50,000 Units and 100,000 Units	31	2.3 days	2 to 4 days	4.4 days	2 to 12 days
IV (a)	Pastilles	4,000 Units	20	3 days	1 to 7 days	8 days	3 to 14 days
IV (b)	Pastilles & Scaling	4,000 Units	20	3 days	1 to 4 days	5 days	3 to 6 days
IV (c)	Pastille Control	—	6	No clinical or bacteriological effect after five days			

Clinically, improvement followed the usual course—pain and tenderness disappearing first; the criterion of complete clinical cure was simply resolution and healing of all the gingival ulcers.

Bacteriologically, it was considered that the use of a platinum-wire loop was a more searching method of testing "bacteriological cure" than the ordinary cotton wool throat-swab: moreover three smears from three separate gingival pockets were made on each examination. During treatment smears were made daily from each case, and treatment was continued until three successive negative reports had been obtained. Almost invariably morphologically typical Treponema Vincenti and fusiform bacilli, with varying numbers of pus cells, were found to persist in the affected pockets for a few days after apparent cure; sometimes they persisted for a week or more, often in large numbers.

The penicillin content of samples of mouthwash, spray and pastilles was assayed at intervals and the results agreed closely with the calculated quantities.*

As a further check on treatment, samples of saliva were taken at fifteen minute intervals after a dose of penicillin from several patients in each treatment group, and assayed to determine how long an effective amount of penicillin (*i.e.* an amount lethal to the standard strain of staphylococcus) persisted.

No penicillin could be detected in the saliva of patients having intramuscular injections.

Patients having one or other of the local forms of treatment gave variable results from case to case; but there was a distinct inverse correlation between the length of time penicillin persisted in effective concentration in the saliva and the length of time elapsing before clinical cure. Thus penicillin was found in effective amounts three-quarters of an hour after a dose in those cases which cleared up in average or less than average time; whereas penicillin disappeared more quickly in those cases which took the longest time to heal. For example in two cases on mouthwash no penicillin could be detected at thirty minutes, and these two took longer to clear up than any others in this group.

Finally an attempt was made to "follow up" all the cases after discharge. Instructions were given for all cases, whenever possible, to report for reinspection one month after discharge, and earlier if any signs of relapse or reinfection occurred.

Four clinical relapses (or reinfections) have been seen so far. They occurred in one month after discharge, 2 after spray, 1 after mouthwash, and 1 after pastille treatment. None has yet been seen after intramuscular injections. It is possible that more relapses (or reinfections) may have occurred.

* See next article by Major K. E. A. Hughes.

In 35 re-inspections at one month none showed clinical evidence of acute ulcerative gingivitis, but in only three cases was a completely negative bacteriological result obtained. In 10, Treponema Vincenti and fusiform bacilli were present (though scanty), and in the remaining 22 they were present in considerable numbers.

DISCUSSION

It would, perhaps, be unwise to draw too many conclusions from our results at this stage, yet the following points appear to have arisen so far.

Intramuscular injections were discontinued after twenty cases; the heavy dosage required to maintain a presumably adequate concentration of penicillin in the blood, and the feeling that this was the least practical method of treatment—necessitating hospitalisation, for example—were the chief reasons for dropping it. We were interested, however, to learn three things: (*a*) that no penicillin reached the saliva: yet (*b*) clinical cure was reached in an average of three days: and (*c*) that bacteriologically this appeared to be the most disappointing form of treatment. Since it is not secreted with the saliva, it might be presumed that parenteral penicillin may not reach organisms more superficially placed in infected pockets.

It seems doubtful if we can yet attach any significance to the apparent absence of relapse in this group, since we cannot be sure that all relapses have been detected.

Between the local forms of treatment there seemed to be little significant difference in effecting clinical cure, $2\frac{1}{2}$ and 3 days being the average time for the gums to heal. Here the controls were of interest; mouthwashes of distilled water containing no penicillin produced cure in 4 to 5 days, whereas plain gelatin pastilles failed to have any demonstrable effect. We could only conclude that the purely mechanical action of the mouthwash was effective.

Local penicillin seems to be preferable to parenteral, and of the three local methods employed, pastilles seem to be the most economical and practical form of treatment since their use would not necessitate admission to hospital.

It is now proposed to compare a series of cases treated by penicillin pastilles with a series treated by one of the older standard techniques. We feel that this is necessary. So far we may say that clinically penicillin "works" in acute ulcerative gingivitis, though not by any means in a dramatic way; moreover, we suspect that relapses may occur after cessation of treatment even when treatment has been prolonged after clinical cure.

It is not proposed here to discuss at length the significance of the bacteriological findings. Perhaps too little is known of the exact

role of the "Vincent's organisms" for any such discussion to pass beyond the realm of speculation. In contrast to the findings of MacGregor and Long (1944) we found that morphologically typical spirochaetes and fusiform bacilli very often persisted for several days after clinical cure in the formerly ulcerated gingival pockets; moreover, they have apparently recurred in the mouths of 32 out of 35 cases re-inspected one month after discharge. (Incidentally, we found in a recent survey of the mouths of 34 Nursing Officers that 20 showed Vincent's organisms although only 3 were clinically affected by acute ulcerative gingivitis. Had swabs been used instead of the loop no doubt many of these collections of organisms would have been missed). The most feasible suggestion is, perhaps, that the penicillin simply failed to reach all the Vincent's organisms in every gingival pocket: but we do not know whether these residual organisms had become penicillin-resistant, whether the patient had become immune (*i.e.* was a carrier), or whether the organisms were avirulent.

MacGregor and Long (1945) consider as a result of their findings that Vincent's organisms play at least a major part in the aetiology of acute ulcerative gingivitis; so far as our work goes the reverse might almost equally well be true.

Acknowledgment and thanks for help are due to Colonel H. T. Higgins, DDS, 21 Army Group; Colonel H. T. G. Wells, OC 75 (Br.) General Hospital; and Major K. E. A. Hughes, OC No. 3 Mob. Bact. Lab.

REFERENCES

MacGregor, A. B., and Long, D. A. (1944), Brit. Med. J., II, 686.
MacGregor, A. B., and Long, D. A. (1945), Brit. Dent. J., LXXVIII, 33.

ULCERATIVE GINGIVITIS: LABORATORY CONTROL

By Maj. K. E. A. Hughes, OC, No. 3 Mobile Bacteriological Laboratory

This work was carried out in conjunction with Maj. A. State, AD Corps, 75 (Br) General Hospital.

A number of penicillin assays were carried out on the saliva of patients undergoing treatment by four methods. The technique used was that described in the "Memorandum on Penicillin Therapy in 21 Army Group", page 74.

Samples of saliva were obtained from those patients given mouthwashes, sprays and pastilles, 15, 30 and 45 minutes *after* the wash or spray, and at the same time *after the finish* of a pastille. The results are shown in the table.

Those patients being treated by continuous intramuscular drip had their salivas examined 1, 2 and 3 hours after the drip was commenced. No inhibition was found in any sample from the ten men concerned.

The figures show that so far as maintenance of bacteriostasis is concerned there was little to choose between the mouthwash and the spray. The pastilles on the other hand did not maintain bacteriostasis for so long. For practical purposes this did not matter as the pastille was sucked continuously, while the washes and sprays were intermittent.

Another point of interest is shown by samples 18, 21 and 26 which were all from the same patient. Bacteriostasis in this case was never maintained for longer than 15 minutes and then only at low titre, suggesting that there was something in his saliva which rapidly destroyed penicillin.

The pastilles used in this preliminary study were home made, and the method of manufacture is given in the appendix. The pastilles made by Burroughs Wellcome were found to last up to three hours in the normal mouth provided they were neither actively sucked nor chewed, and maintained a bacteriostatic level in the saliva for 45 minutes after they were finished.

TABLE

Sample No.	Type of treatment	Concentration of solution in units per cc. or strength of pastille	Assay titres of saliva at minutes		
			15	30	45
1	Mouthwash	250	2	1	0
2	,,	,,	8	8	2
3	,,	,,	3	1	0
4	,,	550	2	1.5	3
5	,,	,,	16	8	2
6	,,	,,	16	16	8
7	,,	,,	6	—	1
8	,,	340	4	1	0
9	,,	,,	8	1	1
10	,,	,,	0	0	0
11	Spray	2750	16	2	1
12	,,	,,	8	1.5	2,5
13	,,	,,	2	0	0
14	,,	,,	4	1	0
15	,,	3370	8	—	3
16	,,	,,	10	1	1
17	,,	,,	6	2	1
18	,,	,,	0	0	—
19	,,	4250	3	1	1
20	,,	,,	4	1	1
21	,,	,,	2	0	0
22	,,	,,	16	2	1
23	,,	8250	16	1	1
24	,,	,,	16	1	1
25	,,	,,	16	1,5	1
26	,,	,,	1.5	0	0
27	Pastille	350	4	1	0
28	,,	,,	1	0	0
29	,,	,,	1	0	—
30	,,	,,	4	1	0
31	,,	,,	4	1	0
32	,,	,,	2	0	0
33	,,	,,	2	0	0
34 — 43	I.M. drip	100,000 per day	No bacteriostasis at 1, 2 or 3 hours		

APPENDIX

PENICILLIN PASTILLES

Required:—

Gelatin: Commercial, pure, Pharmaceutical.
Syrup: Sugar $\frac{2}{3}$, water $\frac{1}{3}$.
Penicillin: Sodium "not for injection", or Calcium } 500 units per pastille.

Method:—

The strength of the gelatin mixture required is:

2 parts gelatin.
2 parts syrup.
1 part water.

Estimate the amount of each required for the batch. Dissolve the requisite amount of sugar in about 50% more water than is required. Add the gelatine and heat until dissolved. Place in 55°C water-bath until volume is reduced to original estimate—about 24 to 36 hours. Add the penicillin, dissolved in a very small amount of sterile distilled water, and pour into flat dish. Place in refrigerator. When sufficiently firm cut to required size: $\frac{3}{8}'' \times \frac{3}{8}'' \times \frac{1}{8}''$. If possible, dry still further in a vacuum dessicator over P_2O_5 until required consistency is obtained, or leave in the refrigerator for a few days before use. It should be possible to obtain a pastille which will last in the mouth for about three-quarters of an hour. For use, one of these should be kept in the mouth *continuously* during waking hours and if the patient happens to awaken during the night he should be instructed to take one.

The pastille should be inserted between the gum and the cheek and allowed to dissolve slowly. It should not be chewed or sucked.

PENICILLIN IN THE TREATMENT OF ACUTE ULCERATIVE GINGIVITIS

By Maj. R. P. Powell, AD Corps, and Capt. J. Colquhoun, RAMC, 105 (Br) General Hospital

GENERAL

A number of patients undergoing treatment for various injuries with intramuscular penicillin were dentally inspected. Almost without exception their mouths and gums were in good condition, even though in some cases there was definite evidence of lack of oral hygiene. As a result of this it was decided to try penicillin in some pathological gum conditions.

Local, rather than parenteral, administration was decided on for the following reasons: —

(*a*) It is economical, and as supplies were limited this was of primary importance.

(*b*) A higher concentration could be maintained in the actual area of infection.

(*c*) It is a less painful method of treatment.

EMPLOYMENT

This report is on the treatment of over a hundred cases of acute ulcerative gingivitis, and the cases chosen were those in which there was marked ulceration with tissue loss, and in which the presence of Vincent's organisms in large numbers could be demonstrated.

ADMINISTRATION

Two series of cases were treated with penicillin—one using an agar pastille (made by Capt. Colquhoun) containing 1000 Oxford units, and the other the commercial tablet (Burroughs Welcome) containing 500 units. These series were compared with a further two series, one being treated with chromic acid and hydrogen peroxide, and the other with a pastille containing agar and sugar only, as a control.

CONTROL TECHNIQUE

The smears were taken with a platinum loop (2mm. in diameter). If this was not sufficiently fine to reach the bottom of the pocket then the straight wire was used.

The quantity of typical Vincent's organisms present was noted as follows:—

+ + + + Lattice work of spirochaetes with very many B. fusiformis.

+ + + Very many spirochaetes and B. fusiformis.

+ + Several spirochaetes and B. fusiformis, roughly 10 per field.

+ A few spirochaetes and B. fusiformis, roughly one per field.

+ Was recorded if a spirochaete was seen in 30 fields.

– Was not recorded unless no spirochaete was seen after searching for at least five minutes.

Also noted was the presence or absence of pus cells, other bacterial flora, and debris.

Smears were taken at 4, 8, 12 and 24 hours after the commencement of treatment and then 24 hourly.

1/100 Flavine and 1% Cetavlon were found to be suitable for sterilising the toothbrushes, as they both: (*a*) do not destroy penicillin; (*b*) sterilise the toothbrush; and (*c*) do not destroy either bristles or nylon.

A mixture of kaolin and calcium carbonate was used for the tooth powder as neither destroys penicillin and they form a satisfactory tooth powder.

The cases were allocated to the various series in the investigation in rotation and not by selection. The two control series (chromic acid and agar and sugar pastilles) were re-allocated to the penicillin series and were subsequently cured.

METHOD OF TREATMENT

This was the same in each of the two series treated with penicillin, except that the different strength pastilles were used.

An outline of the treatment is given:—

First Day.

1. The entire mouth is freed of food debris by swabbing gently with cotton wool, and syringing if necessary with warm water. The entire ulcerated area is then painted with penicillin solution (1000 units per cc.), which is retained in the mouth for three minutes before the patient is permitted to spit out.

2. Tooth brushing is discontinued, and the patient's toothbrush is taken from him and sterilised by soaking for 24 hours in Flavine (1:100) or Cetavlon 1% and then well washed in running water. This sterilisation softens the bristles, which is an advantage, as brushing is restarted very early on in this treatment.

3. Pastille therapy is started, maintaining a pastille in the buccal sulcus opposite the worst area of ulceration continuously throughout the day, except for meal times. Two pastilles are placed in the sulcus just before going to sleep.

Second Day.

Pain will have ceased in most cases. The ulcerated areas are again swabbed with penicillin solution (1000 units per cc.). Gross tartar can usually be removed, and in some cases (if the smears are negative for Vincent's organisms) tooth brushing can be started, using a powder containing penicillin in a base of kaolin and calcium carbonate (1000 units per gm.).

Third Day.

Repeat the swabbing, and continue pastilles until the areas have become epithelialised, and then continue with the tooth powder for at least two weeks.

During the whole period of treatment it is essential that no mouthwashes, gargles, or tooth pastes should be employed as the majority will inactivate the penicillin to a greater or lesser degree, and wash the penicillin out of the mouth.

RESULTS

Series	Aproximate number of hours pastille iasts	Oxford units per pastille	Average number of hours for smears to become negative	Number of hours for slough to disappear	Number of days for ulcer to be completely epithelialised	Remarks
Series treated with chromic acid & H_2O_2	—	—	—	—		In no cases treated with chromic acid was a negative smear obtained. There was a slight drop in the no. of spirochaetes for the first 24 hours which rapidly mounted again
Series on agar & sugar pastille only	$2^1/_2$-3 hrs	—	—	—		There was no change in the bacteriorological pictures, except that there was less debris in the smears
Burroughs Welcome pastilles (500 units)	$1^1/_2$-$2^1/_2$ hrs	500	39.0	44	7.4	
Agar pastilles (1000 units)	$2^1/_2$-3 hrs	1000	20.0	27	5.8	

The following points were noted:—

(*a*) As soon as the spirochaetes, Vincent's or B. fusiformis disappear the pain goes. In no case was a patient free from pain or irritation unless the smear was negative.

(*b*) The penicillin must reach the area concerned and must be maintained there in sufficient concentration. The careful cleansing of the mouth prior to application is of paramount importance, and the initial application penicillinises the local area, the concentration being maintained firstly by the pastilles and later by the use of the penicillin tooth powder.

(*c*) The intelligent co-operation of the patient is essential and treatment must be controlled carefully at every step by the Dental Officer himself, as has been the case in this series.

(*d*) The helpful co-operation of the laboratory is essential, as progress can only be watched accurately from the bacteriological picture. In this investigation *all* smears have been taken by one of us (Major Powell) and examined and reported on personally by the other (Capt. Colquhoun).

(*e*) Any case that has had previous treatment with chromic acid or other caustics reacts less quickly to penicillin, but clears up in just the same manner.

(*f*) No case has been found that failed to react, with the exception of one case (see following case history—Sjt. L.) that required intra-muscular penicillin before yielding a negative swab from every interdental space.

CASE HISTORIES

1. *A typical case.* DVR. T., AGED 39.

9.4.45 Reported to local dental centre with bleeding and tender gums. Treated with chromic acid for three days, with little if any improvement.

12.4.45 Referred to this hospital.

On examination: Deep ulceration around 3, 2, 1/1, 2, 3. Extremely tender. Marked foetor.

Smears taken showed Vincent's organisms + + + +

Routine treatment inaugurated. Smears taken 4, 8, 12, 24, 32, 48 and 72 hours after commencement of treatment, with the following results:—

Initial smear	4 hours	8 hours	12 hours	24 hours	32 hours	48 hours	72 hours
++++	+	–	–	±	–	–	–

Pain ceased after 6-8 hours and the ulcerated area became epithelialised after four days.

Toothbrushing was started after 48 hours and 8/ and /7 were extracted after four days to eliminate pockets. Recovery rapid and uneventful.

2. SJT. L., ROYAL MARINES.

Had had acute ulcerative gingivitis intermittently over a period of 14 months. Had not been clear of ulceration for more than two weeks during this period, though having continuous dental treatment.

On examination: Deep ulceration of palatal and buccal gingival mucosa. Extremely tender, and patient was unable to eat. He was becoming very depressed, and wanted all his teeth extracted.

Routine treatment was carried out, and negative smears were obtained after four days. After six days all the ulcers were epithelialised and the patient stated that his mouth had not felt so comfortable at any time during the preceding 14 months.

After 6 weeks: Patient was still well, but smears were taken as a routine check and were found to show Vincent's organisms + + + +, and on the following day the ulceration started again. He was admitted and given an intensive course of intra-muscular penicillin, as it was felt that there was some pocket not being reached by the local applications. In order to ensure a high concentration in any such pocket 30,000 units penicillin were given intra-muscularly 2-hourly for 48 hours. Further smears were taken from every interdental space at the end of this course. Three of them yielded Vincent's organisms + +, but after a further period of local treatment no Vincent's organisms could be demonstrated in any pocket or interdental space, and at the time of writing this report there has been no relapse (six weeks).

3. L/CPL. P., ROYAL MARINES.

Had acute ulcerative gingivitis since 17.12.44. Treated daily with chromic acid and other caustics at various dental centres. /1 was extracted under N2O on 1.2.45. Condition grew steadily worse. Referrel to this hospital on 5.3.45.

5.3.45 *On examination*: Patient presented a slough inside lower lip the size of a shilling. Socket /1 was filled with foul smelling pus, and the gum margin of all the lower teeth showed marked ulceration. Smears showed Vincent's organisms + + + +.

Treatment: Socket was syringed with penicillin solution (1000 units per cc.) and routine pastille therapy started. Pain went in 24 hours. Ulceration of lower lip and gingival mucosa epithelialised in six days (11.3.45).

17.3.45 $\overline{/1}$ and /2 extracted under N2O and a sequestrum $\frac{1}{2}'' \times \frac{1}{4}'' \times \frac{1}{4}''$ removed. Healing uneventful, dentures were fitted, and there had been no recurrence when seen two months later. This case was astonishing in view of its previous failure to respond to treatment.

RELAPSES

Out of upwards of 100 cases, only eight cases have been seen which relapsed. Other cases from this series may have relapsed, and not been reported to us, but each man was given a proforma to hand to his nearest Dental Officer in the case of a relapse, on which there was a request to inform us of this fact.

In seven of these cases definite pockets had been left, which probably acted as reservoirs of infection. The eighth case was the case No. 2 above (Sjt. L) and it is probable that there was some residual infection remaining deep in an interdental space in his case.

CONCLUSION

1. It is felt that the scheme of treatment described above, using penicillin pastilles, is the best method of treating acute ulcerative gingivitis so far tried. The tooth powder is, we feel, an essential part of the treatment, but is not sufficient of itself to effect a cure.

2. The commercial product (Burroughs Wellcome) is extremely satisfactory in that it is a simple, pleasant form of treatment, well tolerated by the patient. If the treatment is continued for about three days a certain number of patients complain of a chemical irritation of the pharynx which ceases on stopping the pastilles, and is due, in our opinion, to the impure penicillin being used in the manufacture of the pastille.

3. In view of the more rapid cure produced when a pastille containing 1000 units is employed, a result not obtained when using two of the 500 unit tablets, we recommend the manufacture of tablets with 1000 units per tablet.

4. It was found that the thin, rectangular agar pastilles (3 cms. x 1 cm. x 2 mms.) were much easier to retain in the buccal sulcus than the normal round, thick tablet.

5. With an intelligent co-operative patient the B.W. tablet can be made to last two hours, which is sufficiently long for meal

routine. We found the majority of patients could make them last this length of time, and many for longer periods, and as the patients were anxious to get better they refrained from chewing them as a sweet.

6. The penicillin clears up the acute stage quickly and more certainly than any other method of treatment. This enables the routine dental surgery (scaling, gingivectomy and eradication of stagnation areas by extraction) to be done sooner and with no risk of complications due to infection. But this eradication of possible foci of infection is essential in the prevention of relapses. Penicillin is not a substitute for normal dental surgery, but an aid to its rapid and safe employment in these cases.

We wish to acknowledge our thanks for the help and advice given by Lt-Col F. N. Foster, Officer i/c Surgical Division, 105 (Br) General Hospital, and to the staffs of the Pathological Laboratory and Dental Department.

THE EFFECT OF THE LOCAL ADMINISTRATION OF PENICILLIN ON THE CLEARANCE RATE OF DIPHTHERIA CARRIERS

By Lt.-Col. R. E. Tunbridge, RAMC, Officer i/c Medical Division, and Majs. J. H. H. Keall and J. V. Dacie, RAMC, Specialists in Pathology, 110 (Br) General Hospital

The serious loss of man power from diphtheria due to the persistence of positive bacteriological findings, together with the known sensitivity of C. diphtheriæ to penicillin, suggested the investigation of the effect of the local administration of penicillin upon the rate of clearance of diphtheria carriers.

In the absence of any recognised time interval after the onset of the disease before a patient is classified as a carrier, we decided that persistent positive bacteriological findings after the thirty-fifth day of disease constituted a carrier. As far as operational conditions permitted, all carriers so defined were transferred to a selected hospital.

In the initial stages many cases were received with positive bacteriological findings considerably later than the thirty-fifth day. Such cases were used for an introductory study. Later the cases were rigidly selected and controlled and they provided the material for the main investigation.

INTRODUCTORY SERIES

Bacteriological Methods

Nose and throat swabs were plated on blood agar tellurite medium and incubated at 37°C for 48 hours. All suspicious colonies were examined and subcultured on to Loeffler's slopes. These subcultures were examined after 24 hours and in all positive cases the sugar reactions were determined. Virulence tests were not performed as animals were not available.

Routine for Penicillin Therapy

The patients received a spray to the throat two hourly from 0800 hours to 2000 hours daily of a penicillin solution, strength 500 Oxford units per cc., and a three hourly spray up each nostril during the same period. The controlled cases were sprayed with normal saline or distilled water. Swabs were taken from the nose and throat on alternate days first thing in the morning before beginning treatment.

Results

Thirty-seven cases, nineteen on penicillin therapy and eighteen on control therapy, provided the material for this study.

Control Series

Average day of disease on admission to special hospital 52.5 (Max. 86, Min. 40). Total number of days under treatment 430, average 24 days.

Penicillin Series

Average day of disease on admission to special hospital 59.0 (Max. 109, Min. 36). Total number of days under treatment 256, average 13 days.

FULLY CONTROLLED SERIES

Bacteriological Methods

Nose and throat swabs were plated on to a horse blood tellurite medium (a modification of Hoyle's medium) and examined after incubation for 40-44 hours at 37°C. Provisional typing was made upon colonial appearance. A note was made of the approximate number of colonies grown. The diagnosis of C. diphtheriæ was confirmed in all new cases and in every instance where the colonial appearance was unusual or doubtful, by subculture of a colony on to a horse blood agar plate and incubated overnight. Care was exercised to note the presence of hæmolysis. A single colony from the subculture was further subcultured on Lœffler's slopes and incubated overnight, when the morphology was examined after staining by Neisser's method. Finally, the type was confirmed by sugar reactions. Using L.C.C. sugars and glucose broth the reactions were made direct

with material from the Lœffler subculture, but when employing our own sugars—the local sugars did not contain serum—colonies from the Lœffler's slope were first transferred to a serum peptone medium and incubated for six hours; four drops of the latter were then added to the peptone water sugar media.

Virulence tests were not attempted for gravis and intermedius strains, but representative mitis strains were tested. The intradermal method in guinea pigs was employed. All but one of the strains tested were toxigenic.

A few of the diphtheria cultures were tested for penicillin sensitivity and were found to be sensitive.

Routine for Therapy

(*a*) *Penicillin spray for period*: The bacteriological diagnosis was confirmed and the patient given a two hourly spray to the throat from 0800-2000 hours daily for seven days of a penicillin solution, strength 500 Oxford units per cc., and a three hourly spray up each nostril for a similar period. The week's treatment was followed for 48 hours by morning and evening irrigation of the nose and throat with normal saline. First thing the next morning swabs were taken for clearance. If positive bacteriological findings persisted the course was repeated for a second week.

(*b*) *Penicillin lozenge for period*: The bacteriological diagnosis was confirmed and the patient given one penicillin lozenge (500 Oxford units per lozenge), to suck every two hours between 0800 and 2000 hours daily for seven days. The nose was sprayed as in (*a*). The lozenge lasted 30-45 minutes.

Alternate cases were selected as controls and were treated with water, saline, formalin or gentian violet. The routine of the application was exactly the same as for the penicillin treated cases.

Results

The reliability of swabbing: The routine clearance swabs were taken by selected sisters or medical officers. Table I shows the results of taking daily swabs by two people for one week.

TABLE I

Date	250 A		359 B		332 B		188 A		82 B		270 B		207 A		287 B		225 A		330 A	
	Mitis		Gravis		Mitis		Mitis		Gravis		Gravis		Mitis		Mitis		Mitis		Inter-medius	
	N	T	N	T	N	T	N	T	N	T	N	T	N	T	N	T	N	T	N	T
12 March	—	—	O	O	O	4 cols	O	++	+	O	—	—	O	+++	—	—	—	—	—	—
14 March	O	+++	O	O	O	+++	O	+++	O	O	O	+	O	++	O	++	O	++	O	+
15 March	O	+++	—	—	O	+	O	++	O	O	—	—	—	—	O	++	O	O	—	—
16 March	O	4 cols	O	1 col	O	++	O	+++	O	O	O	+	O	+++	O	+++	O	+++	O	+++
17 March	O	+++	O	+	O	++	O	+++	O	O	O	9 cols	O	+++	O	+++	O	+++	O	++
18 March	O	+	O	++	O	++	O	+++	O	O	O	O	O	++	O	++	O	+++	O	+++
19 March	O	O	O	O	O	+++	O	+++	O	O	O	9 cols	O	++	O	+	O	8 cols	O	+++
20 March	—	—	O	O	O	+++	O	+++	O	O	O	+	O	O	O	+	O	+++	O	+++

A = swabs taken by sister. B = swabs taken by medical officer.
If under 10 the actual number of colonies is stated by figure
+ = 10—20 clonies.
++ = 20—100 colonies.
+++ = 100 plus colonies.
++++ = Thousands.

The variations in cases 250 and 287 are considerable, but the variations did not appear to be due to a personal factor. Table II shows the degree of variation obtained on taking swabs from different sites.

TABLE II

Case number	188	197	233	250	287
25/4 Tonsil-Normal method	+++	++++	+++	+++	+++
Superficial	+++	+++	+++	+ (1 colony)	+++
Pharynx	0	+	++	+ (1 colony)	+ (4colonies)
27/4 Tonsil-normal method	+++	++++	++	+	+ (1 colony)
Superficial	+++	+++	++	++	+ (1 colony)
Pharynx	0	+++	0	+++	0
Post-Nasal	0	+ (9 cols)	+ (2 cols)	++++	0
29/4 Tonsil-normal method	++	++++	+++	++++	+ (1 colony)
Pharynx	0	++	+ (1 col)	+	0
Post-Nasal	0	+ (4 cols)	0	++++	0

STANDARD OF CLEARANCE

The variation in the daily swabs led to a critical analysis of the accepted standard for clearance, three negative nose and throat swabs taken on alternate days. In the introductory series several cases yielded a positive result in the week following the obtaining of the requisite number of negative nose and throat swabs. The standard of clearance in the present investigation was three negative nose and throat swabs taken at three day intervals followed by a further nose and throat swab after an interval of one week. This very strict standard has been justified, as 35 cases have yielded a positive swab on the fourth clearance out of 201 proved cases observed.

TYPE OF ORGANISM

In a series of 196 cases (Maj. Dacie) positive cultures were obtained in 138 (Gravis 48, Intermedius 6, Mitis 84). Each patient's strain was repeatedly typed and found to remain constant; thus Pte. Smith's variation of a mitis type retained its peculiarities on repeated swabbings. There was little evidence of cross infection between patients. In only two cases was there any suspicion of a change in the type of organism due to this cause. Nasal infections were uncommon.

RESULTS OF PENICILLIN THERAPY

The results using penicillin spray and lozenge for periods of one and two weeks are given in Table III.

TABLE III

Controls			
One week's treatment	—	Cleared	1
		Failed to clear	45
Two weeks' treatment	—	Cleared	1
		Failed to clear	27
Penicillin Spray			
One week's treatment	—	Cleared	0
		Failed to clear	36
Two weeks' treatment	—	Cleared	3
		Failed to clear	24
Penicillin Lozenge			
One week's treatment	—	Cleared	0
		Failed to clear	21
Two weeks' treatment	—	Cleared	0
		Failed to clear	9

The results show quite definitely that under fully controlled conditions the local application of penicillin, whether in the form of a lozenge or a spray, is without dramatic effect upon the clearance rate of diphtheria carriers. The results from the introductory series where a continuous penicillin spray was used show a slightly favourable effect. There are several very obvious criticisms of the latter results. The treatment was not started at the same time in all cases. Further, some of the penicillin from the previous evening's application might have been present in the throat the following morning, and being taken up with the swab have exercised a bacteriostatic effect upon the culture.

It is not surprising that the local application of penicillin is without dramatic effect upon the clearance rate, if the infection is situated in the crypts of the tonsils. The site of the infection, the bacteriology and histology of the tonsils, and the effect of tonsillectomy on diphtheria carriers are being studied and will be reported in a further communication. The use of parenteral penicillin in the early case has also been studied and has yielded promising results, but until the work has been more fully controlled it is too early to make a pronouncement.

SUMMARY

1. The local application of penicillin, whether as a spray or as a lozenge, was without dramatic effect upon the clearance rate of faucial diphtheria carriers.

2. Evidence is submitted that the standard for the clearance of diphtheria carriers should be three negative nose and throat swabs at three day intervals, followed by a fourth nose and throat swab after an interval of one week.

3. A diphtheria carrier was defined as a case with positive bacteriological findings after the 35th day of disease.

We wish to acknowledge the help of Capt. (Miss) C. P. Larkins, RAMC, Sjt. A. E. Franklyn, Senior Laboratory Technician, and Miss A. Athey, QAIMNS/R. We are also greatly indebted to the encouragement and advice received from Col. R. W. Fairbrother, DDP, 21 Army Group, and Brig. E. Bulmer, OBE, Consulting Physician, 21 Army Group, and to Col. N. Cameron, OBE, for permission to publish.

REPORT ON THREE CASES OF STAPHYLOCOCCAL SEPTICAEMIA TREATED BY PENICILLIN

By Lt.-Col. C. L. Cope, RAMC, Officer i/c Medical Division, and Lt.-Col. G. Macpherson, RAMC, Officer i/c Surgical Division

The following cases of Septicaemia were treated in 79 (Br) General Hospital in Holland:—

CASE (1)—SISTER B.

Admitted 11 January, 1945, at 18.00 hours.

History: Approximately 48 hours ago she ran a wooden splinter into her forearm, just above the wrist. Removed at once. Next morning area extremely painful. Further piece of splinter removed. Pain and swelling increased with general systemic upset, rigors, backache and shoulder pains.

OE. General condition: Very toxic and ill; perspiring, and circumoral pallor. T.101.5°F; P.100; R.22.

Locally: Spreading cellulitis of left forearm with tender enlarged axillary glands. Small puncture wound, scarcely discernible. Wrist movements painful. ? Streptococcal Septicaemia—Blood culture.

Treatment: Continuous penicillin drip, 100,000 units in 24 hours. Sulphathiazole 2 gr. 4 hourly. Locally—foments to forearm. Ichthyol and glycerine to axilla. Copious fluids by mouth.

1800 hours. *Placed on seriously ill list*

12-13 Jan Penicillin drip continued.

13 Jan Slightly improved. Still very ill with pains all over. Pyrexia and toxic appearance. Definite fluctuation posterior aspect forearm near point of entry of wooden splinter. T.102°; P.134; R.24.
Operation (*Statim*) (*in bed*).

Incision of left forearm and evacuation of pus.

18.00 hours. Much worse this evening. Penicillin not producing desired effect. Drip stopped. Total given by drip 220,000 units. Started on "blitz" course of 10,000 units penicillin every ten minutes for 12 doses. Thereafter no penicillin for intermission of 22 hours, when same method was repeated. "Sulpha" crystals in urine; sulphathiazole stopped; dosage given = 21gms. I.V. Saline with alkali commenced.

14 Jan *Placed on dangerously ill list*

14.20 hours. Urine alkaline. No abnormal constituents. T.103°F.; P.120; R.28. Whole blood 2 pints transfused (fresh) in 24 hours. Penicillin 10,000 units every 10 minutes for 2 hours, repeated in evening. Chest —nil gross abnormal.

15 Jan Slightly improved. Drip continued (6% glucose-saline): alkaline drinks. Urine—no abnormal constituents. Penicillin 120,000 units in 2 hours in evening. T.100.8°F; P.108; R.24.

16 Jan I.S.Q. Saline drip discontinued. No penicillin. Swab from abscess—staphylococci, numerous unidentified cocci, and coliforms.

17 Jan Condition not so good. T.101.8°F.; P.100; R.32. One pint fresh blood followed by slow drip 6% glucose-saline (1 pint). Penicillin 100,000 units in 2 hours in evening.

18 Jan Temperature normal. Still has backache. Recommence slow 6% glucose-saline I.V.

This evening she was given a "super blitz" with 500,000 units penicillin in divided doses over 2 hours, as she was definitely worse in spite of normal temperature.

19 Jan 500,000 units penicillin in 2 hours repeated. T.101.5°F; P.100; R.28. Glucose-saline I.V. continued.

20 Jan Still very ill. T.102.5°; P.100; R.26. Has not slept. Fresh blood 20ozs. transfused and then I.V. apparatus taken down. Cellulitis of arm around transfusion area. 500,000 units penicillin in 2 hours administered again.

21 Jan Improved. T.99.4°F; P.100; R.24. Repeat penicillin 500,000 units.

22 Jan Further improvement. T.98.4°F; P.82; R.22. Repeat penicillin 500,000 units.

24 Jan. Much improved, but arm still brawny and swollen. T.P. and R. as on 22 January. Much improved this evening. Penicillin 500,000 units given in 2 hours.

25 Jan Penicillin discontinued. General condition improving. Arm looks better but is still painful.

27 Jan General condition much improved. Apyrexial since afternoon of 22 January.

3 Feb Up for 15 minutes. Condition very satisfactory.

8 Feb Had short walk. Convalescence progressing well.

15 Feb Discharged to Convalescent Home.
Total dosage of penicillin 4,080,000 units.
Total dosage of whole blood 4 pints.
Total dosage of I.V. Glucose-Saline 4 pints.

Needless to say, all other general and local treatments necessary—copious fluids, foments, hypertonic dressings, etc.—were given throughout, but to save space they are not mentioned in detail.

COMMENT

Although no bacteriological confirmation was obtained this case exhibited all the clinical features of a virulent septicaemia, so much so that, at one stage, recovery appeared impossible. In virtue of the fact that no response to normal doses of penicillin was achieved a "blitz" method of administration was instituted. Although some temporary improvement occurred, this was short lived, and only when huge doses of the drug were used did lasting improvement occur.

CASE NO. (2)—CAPT. E. V. B.

History: Onset 16 January, 1945, with severe pain in testes and inner side of thighs, diarrhoea, and a temperature of 105° on first day.

Testicular pain subsided, but pain in adductor regions of both thighs persisted. Temperature swung betwewen 101 and 105° with steady deterioration in general condition until 7th day, when he was admitted to 79th (Br) General Hospital—with no diagnosis.

23 Jan O.E. Very toxic. T.104.5°F.; P.104; R.20. No rash or adenopathy. Spleen not palpable. No signs in heart or lungs. Abdomen mildly distended with gas and slight diffuse tenderness. External genitalia normal. No rectal tenderness or abnormality. There was acute tenderness over the symphysis pubis and along the ramus of the right pubic bone, but no swelling. There was tenderness over the right adductor muscles, but no evident swelling.

Movement of right hip limited by pain, but no joint disease discovered. Small scar on dorsum of right foot which had been septic for two weeks before illness. Urine contained albumen and granular and cellular casts but no pus or organisms.

PROGRESS

Blood culture on two occasions gave a heavy growth of coagulase-positive and penicillin-sensitive staphylococcus aureus. The primary focus was believed to be an inflammation in the region of the right pubic bone, but this never revealed itself more clearly. At no time were any embolic phenomena observed. On 26 January a mild parotitis developed but did not suppurate. On this day treatment with intra-muscular drip of 100,000 units penicillin daily was started and was continued with only one day's break until 12 February, a total of 1.6 million units. The drip was well tolerated and produced a rapid improvement of both general and local symptoms for the first few days, but from 28 January to 13 February the day temperature continued to range between normal and 101°, showing little tendency to further subsidence. On 4 February the tongue became glazed and sore, but responded to nicotinamide. By 11 February the general condition was greatly improved, but there was still some tenderness over right pubic bone. Hip joint movements were now full and painless. Since no further fall in temperature was occurring, "blitz" treatment was instituted. On 14 February a total of 120,000 units penicillin was given in dividend intra-muscular injections at ten minute intervals over two hours, and this procedure was repeated on 15 February, 16 February and 18 February. From the onset of this treatment the temperature never again rose over 99°F.; it remained normal from 17 February until his evacuation to base on 20 February. He has been heard from since, and convalescence had continued without relapse.

COMMENT

The main interest of this case is that continuous intra-muscular drip of 100,000 units penicillin a day did not fully control the temperature, but that "blitz" treatment by 120,000 units in two hours promptly abolished the temperature and removed all symptoms. The contrast between the two modes of treatment was marked.

CASE NO. (3)—SOLDAT P. J. A.

History: Complaints of malaise, headaches and occasional vomiting for several weeks. Then developed cough, pain in chest, and fever. This day for convenience is considered the first day of

disease. He was admitted to 79th (Br) General Hospital on the sixth day with a recorded temperature for the three preceding days which had swung between normal and 105°F. There had been much sweating but no rigors.

On admission: Tongue dry and furred. Mild enlargement of lymph glands in neck and axillae. Soft systolic murmur at cardiac apex. Crepitations heard at left lower lung zone. Urine contained albumen. No other abnormal signs found. White blood cells were 7000 per cmm., with 5200 polymorphs and 1600 lymphocytes. Pulse rate 120; X-ray of chest showed a generalised broncho-pneumonia with most consolidation in left lower lung zone. Blood culture gave a heavy growth of coagulase-positive, penicillin-sensitive staphylococcus aureus.

PROGRESS

Penicillin therapy was started on the 8th day of illness with three hourly intra-muscular injections of 30,000 units. This was continued till the 11th day, when an intravenous penicillin drip was substituted to allow undisturbed sleep; 200,000 units were given by this during the night. General condition had improved but temperature continued to swing from normal to 104°F. No penicillin was given on the 12th day. On the 13th day a form of intermittent "blitz" treatment was started, 200,000 units being given intravenously in 3-4 hours. This was repeated on the 14th day, and the temperature fell to 99-100°. On the 16th day 400,000 units were given intravenously in 4 hours, but the temperature again rose to 103°. Doses of 200,000 to 300,000 units were given in this manner on the 17th, 18th and 19th days, but the temperature nevertheless returned to 105°. The general condition did, however, tend to improve during the penicillin therapy and to deteriorate when it was withheld. There was no appreciable change in physical signs, and no embolic phenomena were observed.

The third phase of treatment was started on the 22nd day, a fresh continuous intravenous drip of concentrated solution being set up. By this two million units were successfully given in 5 days. There was some subjective improvement. During this phase the temperature swung between normal and 102°, but immediately penicillin was stopped it returned to 105°. On this, the 27th day, he was evacuated to base.

He had had treatment in various ways with a total of 4.9 million units for a penicillin-sensitive staphylococcal infection without any appreciable improvement in his condition.

Fresh X-rays of the chest on the 22nd day showed that the pneumonia was resolving. The apical systolic murmur did not change appreciably during his stay in this hospital, and the pulse remained about 120 throughout.

COMMENT

Because of the failure to respond it was suspected that a staphylococcal endocarditis was present and that the development of more definite signs of this was being prevented by the penicillin. It was clinically unlikely that the broncho-pneumonia was the cause of the sustained septicaemia. It appeared that this man could only be maintained alive by continued heavy penicillin dosage, and the question how long such therapy should be continued raised an interesting and difficult problem. The further history of this case is not known.*

CONCLUSIONS

It would appear that in cases of septicaemia where the ordinary course of penicillin therapy is failing to control the infection, a "blitz" technique is always worthy of a trial.

Besides cases 1 and 2 reported here, several casualties with severe infection following wounds in battle have been treated by "blitz" methods in the Surgical Division of this hospital. In most cases penicillin therapy controls the temperature, but where the toxaemia has been profound, and where presumably the organism has been less sensitive to penicillin, the "blitz" method has been necessary to achieve the best clinical results. In all these cases response to the latter method has been immediate, even if ordinary penicillin therapy had previously failed.

As Case No. 3 did not respond, the assumption is that the patient had developed a bacterial endocarditis.

SUMMARY

(1) Three cases of septicaemia are reported.

(2) No definite conclusions can be drawn from such a small series, but in severe infections if the response following ordinary dosages of penicillin is unsatisfactory "blitz" tactics (intensive or super-intensive therapy) may produce the desired results. The method consists in giving large doses over short periods by frequent injections, and these are repeated at 1-2 daily intervals for as long as is necessary.

Our thanks are due to Col. C. E. Eccles, OBE, for permission to publish these records.

* Editorial Footnote: By mid April, 4 weeks after transfer, this patient had improved considerably; a positive blood culture of a coagulase-positive, penicillin-sensitive staphylococcus aureus was obtained once in the base hospital, and thereafter cultures were negative. His lung condition had cleared up, but the systolic apical murmur persisted. He was still receiving penicillin therapy, with occasional intermissions in administration.

STAPHYLOCOCCUS PYOGENES SEPTICAEMIA TREATED WITH PENICILLIN

By Lt.-Col. Leonard Howells, RAMC, Officer i/c Medical Division, 106 (Br) General Hospital, Maj. R. R. Hughes, RAMC. Medical Specialist, and Capt. R. Rankin, RAMC, Pathologist

The following is an account of two cases of staphylococcus pyogenes septicæmia treated with penicillin:—

CASE 1. Marine A. E. W. (aged 22 years). On 28 September, 1944, he developed heachache, sweating, slight cough, and pain in the back; admitted to sick bay the following day.

30 Sep Admitted to hospital still complaining of the above symptoms. T.101.6°F: P.100: R.22. Throat slightly injected. No other abnormality found. Rather apathetic.

1 Oct Condition had deteriorated; swinging a temperature of 102°F, and pulse and respiratory rates rising. Confused, restless and irritable. Heart—nil gross abnormal. Some neck rigidity and a slightly positive Kernig's sign. In view of these findings a clinical diagnosis of meningococcal meningitis was made. Lumbar puncture done under pentothal anæsthesia; pressure 200mms. and fluid slightly murky; it had 40 red and 9 white blood cells per cmm., 40mgms.% of protein (no excess of globulin, 70mgms.% glucose and 700mgms.% chloride). The urine was loaded with albumin (0.75gms. Esbach) and on microscopical examination scanty epithelial cells, leucocytes and granular casts were found. Blood examinations; HB. 89%; R.B.Cs. 4,750,000 per cmm.: W.B.Cs. 14,000 per cmm, with 85% polymorphonuclears.

2 Oct Patient still confused and irritable, with temperature swinging to 102°F and raised pulse and respiratory rates. Neck rigidity and Kernig's sign more marked, fundi normal, all tendon reflexes absent, and plantar responses showed voluntary withdrawal of both feet. Heart now enlarged, with apex beat $4\frac{1}{4}''$ from the mid line in the 5th intercostal space; a systolic murmur was audible at apex and base, and B.P. was 140/60. The white cell count had now risen to 23,600 per cmm. with 84% polymorphs. Blood urea 55mgms.%. Urine still loaded with albumin; leucocytes and granular casts present.

Pulse rate rose steadily during day and at 2200 hours was 142 per minute. At this time he suddenly developed a left hemiparesis involving the limbs and face, and on examination his heart was found to be more dilated. It was now felt that a clinical diagnosis of infective endocarditis could be made; although this had not yet been confirmed by blood culture the dangerously ill condition of the patient made immediate specific treatment essential. Treatment with penicillin was therefore commenced; he was given 100,000 units at 2330 hours followed by 40,000 units intra-muscularly 3 hourly day and night.

3 Oct By 0900 hours he had been given 220,000 units of penicillin. His general condition had improved somewhat and his pulse rate had fallen to 108 per minute, but he was still in a state of low muttering delirium, his neck rigidity was more marked and his hemiplegia unchanged. Urine loaded with albumin, blood urea 80mgms.%, and the cerebro-spinal fluid now contained 376 red blood cells per cmm. Blood and cerebro-spinal fluid cultures were taken on this date and from both a smooth-growing well pigmented strain of staphylococcus pyogenes was isolated after 36 hours. The organism was coagulase-positive, moderately hemolytic, and showed a sensitivity to penicillin equalling that of the standard "Oxford" strain. When re-examined at 1900 hours he was still delirious, the neck rigidity and hemiparesis were still marked although he could now use his left arm a little, his apex beat was $1''$ outside the left mid-clavicular line in the 5th intercostal space, and a soft apical diastolic murmur could now be heard. The spleen was not palpable.

4 Oct General improvement in the patient's condition: temperature in region of 99°F and pulse steadily falling. Still delirious, however, and neck rigidity and

hemiparesis were severe: heart condition unchanged. Blood urea 60mgms.%.

5 Oct Temperature normal, and pulse and respiratory rates falling rapidly. Still very ill but condition had improved and he was now having short lucid intervals. A crop of purpuric spots had appeared on the toes of both feet. The cerebro-spinal fluid pressure was 250mms., and it contained 167 red blood cells per cmm.: culture sterile. By 2030 hours he had been given 1,020,000 units of penicillin, his condition was rapidly improving, he was fully conscious with only occasional short periods of confusion and was able to use his left hand to hold a feeding cup.

6 Oct Patient much better; afebrile for 24 hours. Slight delirium occasionally. Neck rigidity more marked. Hemiparesis improving. Left extensor plantar response. Apex beat still well outside mid-clavicular line: soft localised aortic systolic murmur and a harsh apical diastolic murmur. Liver and spleen not palpable. Blood urea 55 mgms.%: urine contained some albumin, leucocytes and an occasional granular cast.

7 Oct Now using left arm and leg a good deal although weakness persisted; condition otherwise unchanged.

8 Oct An aortic diastolic murmur was now heard for the first time. White blood count 14,150 per cmm.: 81% polymorphs. Course of oral sulphapyridine commenced with an initial dose of 2gms., followed by 2gms. 4 hours later, then 1gm. 4 hourly.

9 Oct General condition now very good; appetite good; sleeping well; very occasional short periods of delirium. Occasional rise of temperature to 99° or 100°F. Apex beat was in mid-clavicular line in the 5th left intercostal space; no palpable thrill; rough aortic systolic murmur conducted along the subclavian and carotid arteries and also a soft short aortic diastolic murmur conducted down the left border of the sternum. The pulse was collapsing, the blood pressure 140/40, and there was a pistol-shot murmur audible over the femoral arteries. Spleen not palpable. Now using left arm normally, but there was a slight weakness of the left lower face, a spastic left leg and a left extensor plantar response. Abdominal reflexes present but diminished on the left side. Blood urea 45mgms.%. X-rays showed definite cardiac enlargement to the left with the general configuration of an early aortic lesion; and some hyperæmia at the base of the right lung.

10 Oct Still improving. Neurological signs almost completely cleared. A number of large hæmorrhagic blisters appeared on the hands and feet. Red blood cells were found in the urine for the first time.

12 Oct Total of 3,020,000 units of penicillin now given; drug discontinued.

18 Oct Condition excellent; afebrile for past 7 days. Still slight weakness of left face. Aortic bruit unchanged and heart still enlarged, but sounds much stronger. The blood count showed Hb. 79%, R.B.Cs. 3,700,000 and W.B.Cs 10,600 per cmm., with 68% polymorphs. Blood sedimentation rate 4mms. in 1 hour. Urine: a few leucocytes, red cells and granular casts. Sulphapyridine discontinued after a total dosage of 50gms.

6 Nov Patient feeling very well; appetite good and sleeping well. Afebrile since Oct 11 but pulse rate still 90 to 100 per minute. Slight weakness of the left lower face; left arm and leg both normal and plantar response flexor. Apex beat diffuse and heaving, 4″ from the mid line in the 5th left intercostal space. Rough systolic bruit audible over whole præcordium but loudest in aortic area and conducted slightly along carotid and subclavian arteries; also soft diastolic bruit over whole præcordium, loudest in pulmonary area. Lungs and abdomen normal, and spleen not palpable. Blood sedimentation rate 0.5mm. in 1 hour; Kahn test negative, and blood showed Hb. 85%; R.B.Cs. 4,010,000 and W.B.Cs. 9,300 per cmm. with 69% polymorphs. Pulse collapsing in type, blood pressure 150/30 and there was a pistol-shot murmur audible over both brachial and femoral vessels.

7 Nov Evacuated to the United Kingdom.

DISCUSSION

This was a typical case of infective endocarditis due to staphylococcus pyogenes treated with penicillin and sulphapyridine. No primary focus was found, nor any history suggestive of a staphylococcal infection. The diagnosis was at first obscured by a subarachnoid hæmorrhage and a hemiparesis, presumably the result of rupture of a mycotic aneurysm; by the fifth day of the disease, however, the cardiac changes were sufficiently definite to suggest the diagnosis, and this was confirmed later by isolation of the organism from the blood and cerebro-spinal fluid. Penicillin treatment was commenced on the fifth day of the

disease and within 52 hours the temperature had fallen to normal. A total of 3,020,000 units were given over a period of 9 days, but as he still showed occasional rises of temperature this was followed by a course of 50gms. of sulphapyridine.

During the early stages of the illness the patient had the usual features of a septicæmia. Following treatment these subsided and when discharged on the 40th day of the disease the temperature had been normal for 26 days, the white cell count was 9,300 per cmm., the hæmoglobin had risen to 85% and the blood sedimentation rate was 0.5mms. in 1 hour. One unsatisfactory feature was a pulse rate remaining persistently at the 90 to 100 level despite complete bed rest.

The embolic phenomena were of particular interest. On the day following admission to hospital the patient was noted to have signs of slight meningeal irritation and on lumbar puncture his cerebro-spinal fluid was found to contain 40 red blood cells per cmm. The meningeal signs gradually increased in severity and 24 hours later he suddenly developed intense neck rigidity, a left hemiparesis, and the cerebro-spinal fluid now contained 376 red cells per cmm. The neck rigidity gradually subsided during the following week. The hemiparesis was more persistent, but all that ultimately remained was slight weakness of the left lower face and minimal changes in the reflexes on the left side. It seems likely that the patient had an infected cerebral embolus which produced a mycotic aneurysm very early in the course of the disease, leaking slightly at first, and later more severely to produce a focal cerebral lesion. Other embolic manifestations were a crop of purpuric spots and later a large number of hæmorrhagic vesicles which appeared on the toes and feet. Osler's nodes were not seen, there were no retinal emboli, and no splenic enlargement.

The renal changes provided some interesting and confusing features. At the time of the intracranial hæmorrhage (4th day) there was heavy albuminuria with granular casts in the urine, and a blood urea estimated two days later at 80mgms.%; such changes are not uncommon with acute intracranial conditions like hæmorrhage and meningitis and are apparently not associated with renal damage. Together with the mental disturbance they raised the possibility of uræmia at that stage of the illness. The urine was examined for red blood cells each day but these were not found until the 13th day; by this time the blood urea had fallen to 45 mgms.% and there remained only a trace of albumin together with granular casts in the urine. These later changes were probably due to an embolic focal nephritis and persisted for some time.

When questioned later the patient admitted to an attack of "rheumatism" in childhood. This seems to have left no gross cardiac lesion as he could exercise without undue discomfort and no heart lesion was discovered at several medical examinations during his naval service. On admission to hospital his heart was clinically normal, during the acute stages of the disease it rapidly enlarged, various changing murmurs were produced, and on the 5th day of the illness the blood pressure was 140/60; it was not until the 11th day that an aortic diastolic murmur was heard and by the following day he had the classical features of an aortic regurgitation. It seems possible that there may have been some slight rheumatic damage to the aortic valve which determined the localisation in this situation and that this damage was much increased by the present illness. As the septicæmic condition subsided the heart diminished in size and the murmurs became less intense, but at the time of evacuation he undoubtedly had a severe aortic leak.

In view of the short period of observation the man cannot be regarded as certainly cured, but we feel this result is most encouraging and that penicillin is worthy of trial in other similar cases.

CASE 2. Sapper E. G. B. (aged 24 years) was admitted to hospital on 27 August, 1944. His illness commenced on the 21 August with a sore throat, fever and general malaise.

27 Aug On admission he looked ill; T.103°F; P.100; R.25. Tonsils considerably enlarged, œdematous, and covered by a yellowish follicular exudate. No abnormal signs in heart, lungs, abdomen or central nervous system. A throat swab showed Vincent's organisms and a few gram-positive cocci, and on culture non-hæmolytic streptococci and a scanty growth of staphylococci were obtained; no K.L.B. He was given sulphanilamide 2gms. initial dose, followed by 1gm. every 4 hours.

28 Aug He had two rigors, the temperature reaching 103.8°F.

29 Aug Slight deterioration in general condition; no change in appearance of throat; decrease in fever during day. Pleural friction rub heard in right axillary region. Urine contained trace of albumin. Blood film showed no malarial parasites. Total white cell count 7,200 per cmm., with 50% polymorphonuclears, 8% small lymphocytes, 30% large lymphocytes, and 12% monocytes. He had now received 12gms. of sulphanilamide with no apparent improvement so it was decided to substitute sulphathiazole 1gm. every 4 hours instead.

30 & 31 Aug Fever varied from 97°F to 103°F; pulse rate rose to 128 per minute, and he was now seriously ill with no change in the condition of the throat.

1 Sep Spleen palpable clinically for first time; the pleural friction rub persisted; sputum became blood-stained. Tonsils still greatly enlarged and covered by yellowish exudate. Sputum examination for tubercle bacilli negative.

2 Sept On blood culture a good growth of staphylococcus pyogenes was obtained (confirmed by another culture 2 days later). The organism had the following characteristics:—A smooth, moderately-pigmented strain of staphylococcus pyogenes, non-hæmolytic, coagulase-positive; penicillin sensitivity equal to that of the standard "Oxford" strain. It was now clear that the patient had a general septicæmia, and in spite of having received 12gms. of sulphanilamide and 25gms. of sulphathiazole he was getting steadily worse. Sulphathiazole treatment was stopped and at 2200 hours penicillin was given instead, in doses of 16,660 units by intra-muscular injections every 3 hours. The temperature at 2200 hours was 102°F and the pulse rate 110 per minute. No pathogens were obtained from culture of a throat swab. The total white cell count was still relatively low considering the nature of the infection, namely 6,800 per cmm. with 50% polymorphonuclears, 27% small lymphocytes, 19% large lymphocytes, and 4% monocytes.

3 & 4 Sep Slight lowering of temperature and some improvement in general condition apparent.

5 Sep The temperature dropped to normal and was accompanied by a striking improvement in the general condition of the patient and in the local appearance of the throat. Spleen no longer palpable and pleural friction rub could not be heard. Subsequent progress:—There was a rise of temperature to 100°F on the 6th and 7th September and to 99°F on the 9th and 10th September, but after this the temperature and pulse rate remained at normal levels. Penicillin was discontinued on 11 September (total given 1,133,288 units). By this time all clinical evidence of septicæmia had disappeared and the appearance of the throat was normal. Further recovery uneventful. No residual signs of disease in any system. Evacuated to UK for a period of convalescence, 20 September, 1944.

DISCUSSION

This was a case of staphylococcus pyogenes septicæmia associated with acute tonsillitis. The resistance of the patient against the infection was poor as was evidenced by a serious deterioration in his clinical condition and by the unsatisfactory white blood corpuscular response. Treatment with 12 gms. of sulphanilamide followed by 25gms. of sulphathiazole failed to produce any improvement in the local tonsillar infection or in the general condition. Penicillin was administered at a critical stage of the illness, and within 56 hours was followed by a dramatic improvement, and a few days later by a complete and uncomplicated recovery.

CONCLUSION

The above two cases present encouraging features in the treatment of staphylococcus pyogenes septicæmia with penicillin. In the first case the favourable result was probably assisted by sulphapyridine therapy, but in the second case sulphanilamide and suphathiazole each failed to produce any improvement in the condition.

SUPPLY AND DISTRIBUTION OF PENICILLIN IN 21 ARMY GROUP

By Col. R. W. Fairbrother, DDP, 21 Army Group

The provision of penicillin to medical units, particularly during the early phases of the campaign, presented many serious problems to the planner. It was anticipated that there would be a large number of casualties during the assault on the Continent and that practically all would be transported back to UK, often under conditions unsuited for adequate medical treatment. At a later stage, a rapidly extending L of C had also to be considered. Moreover supplies of penicillin were, at the time, strictly limited, medical units were likely to be widely distributed and often very difficult to contact owing to transport limitations, while the stability of penicillin was then uncertain and conservation at low temperatures was recommended.

In view of the great potentialities of penicillin in wound prophylaxis, it was, however, considered essential that all severely wounded cases should receive an adequate dosage at the earliest opportunity and that further doses should be given at regular intervals throughout the various stages of the L of C. The following arrangements to accomplish this were made by the DDP (Col. J. S. K. Boyd) and the Consulting Surgeon (Brig. A. E. Porritt).

An Adviser in Chemotherapy and Penicillin was appointed to control, and advise on, the use of penicillin, while No. 3 Mobile Bacteriological Laboratory was reserved solely for penicillin investigations. Problems arising in the field were investigated immediately and much valuable information, particularly with regard to technique of administration, was thereby obtained. These investigations are reported elsewhere in detail by Maj. K. E. A. Hughes. The main distribution of penicillin was made by No. 1 Base Transfusion Unit, directly to base units and through the Advanced Blood Banks in the case of the forward units.

In the early phases, the policy was early evacuation of casualties from the beach head to UK by LST and hospital carrier and then to EMS hospitals by ambulance train. This entailed repeated injections of penicillin during transit often under extremely difficult conditions. In order to ensure that injections could be carried out at all stages, supplies of penicillin and distilled water were allotted to the various units involved, such as CCS, FDS, ASC, CEP, FSU, LST,* hospital carriers and ambulance trains. Stocks were replenished daily. The penicillin was at first the sodium salt of British manufacture prepared in tablet form, each tablet containing 7500 units. Later American preparations were used; these were in powder form in ampoules containing 100,000 units. Supplies were distributed by No. 1 BTU who were issuing transfusion supplies daily to FTUs via the Advanced Blood Banks. Bottles containing sterile distilled water (5 and 10 ml) were supplied with the penicillin.

A standard dose of 90,000-100,000 units was given initially, further doses of 45,000-50,000 units being administered at intervals of 5-6 hours. A bacteriostatic level in the blood was thus maintained throughout the journey. A special yellow penicillin tie-on label, prepared by the MRC, was fixed in a conspicuous position on the patient so that indications for, and the time of, further dosage could be readily obtained. The continuation doses were given by MOs on LSTs, carriers and ambulance trains.

At a later stage, when more general hospitals became established in the theatre, it was possible to adopt a holding policy for casualties. This called for a modification in the administration of penicillin. Repeated intramuscular injections to large numbers of patients require much time and attention and this procedure is impracticable during busy periods. Penicillin was consequently given by the continuous drip method when casualties were held in hospital or CCS; this method required relatively little attention by the medical and nursing officers,

* ASC = Advanced Surgical Centre.
BTU = Base Transfusion Unit.
CCS = Casualty Clearing Station.
CEP = Casualty Evacuation Point.
DDP = Deputy Director Pathology.
EMS = Emergency Medical Service.
FDS = Field Dressing Station.
FSU = Field Surgical Unit.
FTU = Field Transfusion Unit.
L of C = Line of Communication.
LST = Landing Ship Tank.
MO = Medical Officer.
MRC = Medical Research Coucil.
RAF = Royal Air Force.
REME = Royal Electrical Mechanical Engineers.

the patient being instructed to watch the drip chamber and draw the attention of the medical staff if the drip ceased. The dosage was 100,000 units in 1 pint of saline or distilled water over a period of 24 hours. Several giving outfits were tried, including Eudrip III, and it was found that, for use under field conditions, a saline giving outfit with a special time strip was the most satisfactory type. This has been used extensively with good results. In some cases penicillin drips were functioning during the transfer of cases by ambulance from CCS to general hospitals. These proved satisfactory but they are now seldom used as a trained orderly is required to ensure the continuous working of the outfit during the journey.

These two methods of intramscular injection, viz., repeated single doses and continuous drip, have been used throughout the campaign for parenteral inoculations.

In the early stages penicillin was reserved mainly for the severely wounded but later, as supplies increased, it was possible to apply this agent to the treatment of medical, dermatological and venereal cases. A marked saving in man-power has resulted.

Penicillin in powder form was used in increasing quantity as the campaign progressed. This was prepared for forward units by No. 3 Mobile Bacteriological Laboratory and distributed daily during the active periods by the blood transfusion service. In general hospitals, this powder was prepared by the pathologist for local use. Penicillin-sulpathiazole powder has now become available from proprietary sources. The powder was given by means of the RAF pattern insufflator, a type of which was made in the theatre by REME.

This general scheme of supply and distribution worked satisfactorily throughout the campaign and, while at times casualties were heavy, no unit was ever short of penicillin for essential requirements.

INACTIVATION OF PENICILLIN BY HUMAN SERUM

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

In their earlier descriptions of its properties Florey and his collaborators stated that human serum does not inactivate penicillin (Abraham et al, 1941). Bigger (1944), however, produced evidence that at body temperature the action of penicillin is in fact inhibited by human serum.

In view of these apparently contradictory statements an investigation was undertaken to obtain further evidence as to what really did happen, and to try to correlate the results with the bacteriostatic levels obtained in the blood of patients under treatment by continuous intramuscular drips of 100,000 units per day. Accordingly these patients had 10 to 20 ccs. of blood taken by venepuncture before their intramuscular drips were set up. The syringes and needles were sterilised in the autoclave and the blood when taken was transferred with all sterile precautions to dry, sterilised, universal containers. No sample became infected during the course of the experiment. In all 18 samples of blood were examined, and in 14 of these a comparison was made with the bacteriostatic blood level achieved during treatment.

METHODS ADOPTED

1. Barium penicillin of known strength (58.5 units per mgm.) was dissolved in sterile distilled water to give a solution of 20 units per cc. This was dissolved 1 in 10 with the serum under test to give 2 units of penicillin per cc. in 90% serum.

The barium salt was used in preference to the sodium as it was known to be stable in solution, and was in fact the standard used in all assays at that time. An immediate assay was carried out as soon as the mixture was made and the remainder of the sample divided into two equal parts, one of which was placed in the incubator at 37°C and the other in the refrigerator at 2-4°C.

After exactly 24 hours these two specimens were reassayed.

At the same time a control of the barium penicillin in sterile distilled water was made up. This was also assayed straight away and then put into the incubator for 24 hours. It was not considered necessary to put part of the control in the refrigerator as it was known that its stability at that temperature was absolute for a much longer period than 24 hours. It was in fact an identical solution with the standard in use at that time.

2. The assay of the penicillin serum mixtures was carried out by the standard "Oxford" plate method.

3. The bacteriostatic blood levels were carried out by Heatley and Garrod's technique using a 1 in 10 dilution of normal serum as the diluent.

As the investigation was to test the effect of serum on penicillin it was thought possible that it might be advisable to use some other diluting fluid rather than serum for the bacterostatic tests.

Consequently a few tests were put up in duplicate using 1 in 10 serum and broth as the diluents. It also became necessary to ascertain whether broth itself had any deleterious effect on penicillin under the conditions of the main investigation. This was carried out as follows:—

A stock solution of penicillin containing 1000 units per cc. was made in distilled water. From this, two series of dilutions were made to bring the final strength to 2 units per cc. The diluents were distilled water and broth respectively. The small amounts of distilled water carried down in the broth series was considered too small to influence the result.

The broth and water dilutions were assayed immediately they were made and divided into two parts, one being placed in the incubator and one in the refrigerator.

The experiment was repeated using different batches of broth as diluting fluids, but the results were constant.

Two sample titrations are shown in Table I.

TABLE I

Sample	Solvent	Original titre Units/cc	Titre after 24 hours 2–4° C	Titre after 24 hours at 37° C	% loss of 2-4° C spec as compared with orig.	% loss of 37° C spec. as comp'd with orig.	% loss of 37° C spec. as com'd with 2–4° C
1	Broth	2	2	1.25	0	37.5	37.5
	Water	1.2	1.25	0.6	0	50.0	52.0
2	Broth	1.0	1.5	1.1	0	0	27
	Water	1.4	2.0	1.5	0	0	25

From these results, it appeared that broth per se did not destroy penicillin under the conditions of the experiment, any losses being explained by the temperature at which it was carried out.

This being so, bacteriostatic blood levels were ascertained in 18 patients using broth and 1/10 serum as diluting fluids, with the results shown in Table II.

TABLE II

Serum No.	Bacteriostatic dilution	
	Serum diluent	Broth diluent
1	1/1	1/1
2	1/1 (partial)	0
3	1/1 (1/2 partial)	1/1
4	1/1	1/1 (partial)
5	1/8	1/8
6	1/1	1/1
7	1/1 (1/2 partial)	1/2 (1/4 partial)
8	1/2	1/2
9	1/4	1/4
10	1/64	1/32 (1/64 partial)
11	1/8	1/8
12	1/8 (1/16 partial)	1/8
13	1/32	1/32
14	1/64	1/32
15	1/16 (1/32 partial)	1/4 (1/8 partial)
16	1/64 (1/128 partial)	1/128
17	1/128	1/64 (1/128 partial)
18	1/8	1/16

It will be seen from Table II that broth and serum gave identical results 7 times, that serum gave a slightly higher titre 8 times and broth 3 times. For practical purposes there seemed to be little to choose between the diluents. However, the colonies in the broth specimens tended to be smaller and more difficult to see, and also as contaminants are less likely to grow in serum, it was decided to use 1/10 serum as the diluting fluid in the experiment.

Table III shows the results of the various assays of the penicillin-serum mixtures and controls and the bacteriostatic level found in the patients from whom the test sera had been obtained.

TABLE III

Serum No.	Assays of serum penicillin mixture in units per cc.			Assays of controls in units per cc.		Percentage loss of potency				Patient's bacterio-static level	Hours specimen taken after drip started
	Immed-iate	2-4° c	37° c	Immed-iate	37° c	Immediate compared with theoretical	37° C compa-red with immediate	2-4° C compared with immediate	Control at 37° C compa-red with imm. control		
1	1.5	1.2	0.35	1.9	1.75	25	77	20	8	—	—
2	1.4	1.75	0.35	1.9	1.75	30	75	0	8	—	—
3	1.25	1.5	0.7	1.9	1.75	37	44	0	8	—	—
4	1.2	1.75	0.55	1.9	2.0	40	54	0	0	1/1	18—24
5	1.2	1.3	0.45	2.0	1.5	40	62	0	25	1/1	12—18
6	1.25	1.25	0.6	1.5	1.9	37	52	0	0	1/4	18—24
7	1.25	1.25	0.4	1.5	1.9	37	68	0	0	1/1	12—18
8	1.6	1.25	0.8	2.0	1.8	20	50	22	10	1/1	96
9	1.4	1.2	0.5	2.0	1.8	30	64	14	10	1/1	12—18
10	1.5	1.25	0	1.75	1.0	25	100	17	43	1/2	12—18
11	1.5	1.25	0.4	1.75	1.0	25	73	17	43	1/1	12—18
12	1.6	1.4	0.6	1.6	1.2	20	62	12	25	1/2	48
13	1.6	1.25	0.8	2.0	1.8	20	50	22	10	1/1	96
14	1.5	2.0	0.5	1.75	1.55	25	67	0	11	0	12—18
15	1.25	1.2	0.75	2.0	0.5	37	40	30	75	1/2	36
16	1.7	1.6	0.6	2.0	0.5	15	65	6	75	1/2	72
17	1.5	1.1	0.55	2.0	1.4	25	63	27	30	1/8	12—18
18	1.45	1.25	0.4	2.0	1.4	28	73	14	30	1/1	18—24

SUMMARY OF TABLE III: Serum	Immediate	Average loss 29%	Range 15— 40%
	2—4° C	Average loss 11%	Range 0— 30%
	37° C	Average loss 63%	Range 40—100%
	Control 37° C	Average loss 23%	Range 15— 40%

Study of Table III shows:—

1. Although 2 units per cc. of penicillin were added to the serum, the immediate assay value shows a lower figure. The fall is greater than can be explained by the inherent inaccuracies of the method. It averages 29% with a range of 15-40% for the whole series.

The true explanation probably is as follows: During the process of assay the serum-penicillin mixture is subject to a temperature of 37°C during incubation overnight. Consequently the serum is acting on the penicillin for the whole of that period and therefore a lower value than the theoretical 2 units per cc. is found. This fact also affects the results of the assays of the other serum-penicillin mixtures.

2. The average loss of potency for the serum-penicillin mixture kept at 37°C for 24 hours was 63% (range 40-100%) when compared with the "immediate" assay value. This was considered a fairer assessment than comparison with the "theoretical value" of 2 units per cc. as the effects of heat during the actual process of assay of the immediate specimen and the 24 hour specimen cancel each other to some extent.

3. The average loss for the aqueous solutions under the same conditions was only 23% (range 0-75%), therefore the 63% loss in (2) is not due to heat but to a combination of serum and heat.

Why this range of 0-75% is so large is not at present understood. The watery solutions were always kept in small screw-capped glass bottles of the same type and were made up with approximately neutral distilled water. A closer range and smaller loss was expected.

4. The average loss of the serum-penicillin mixture kept in the refrigerator was 11% (range 0-30%).

These findings corroborate those of Lt.-Col. Bigger, RAMC, that at 37°C, serum has a definite inactivating effect on penicillin. The loss of potency cannot be explained by the temperature alone, as the aqueous solutions under the same conditions only deteriorated by 23% as compared with 63% for the serum mixtures.

At refrigerator temperature serum has little effect on penicillin, the loss of 11% potency being within the margin of experimental error of the technique.

5. The bacteriostatic level in the patient's blood during treatment appears to have little relation to the inactivating power of

the serum, probably because this effect which is progressive with time (see below) is swamped by the rate of excretion. The blood samples were taken at different times during the course of treatment varying from 12 to 96 hours.

Table IV correlates the serum assay titres after 24 hours at 37°C, the percentage loss of potency and the bacteriostatic level.

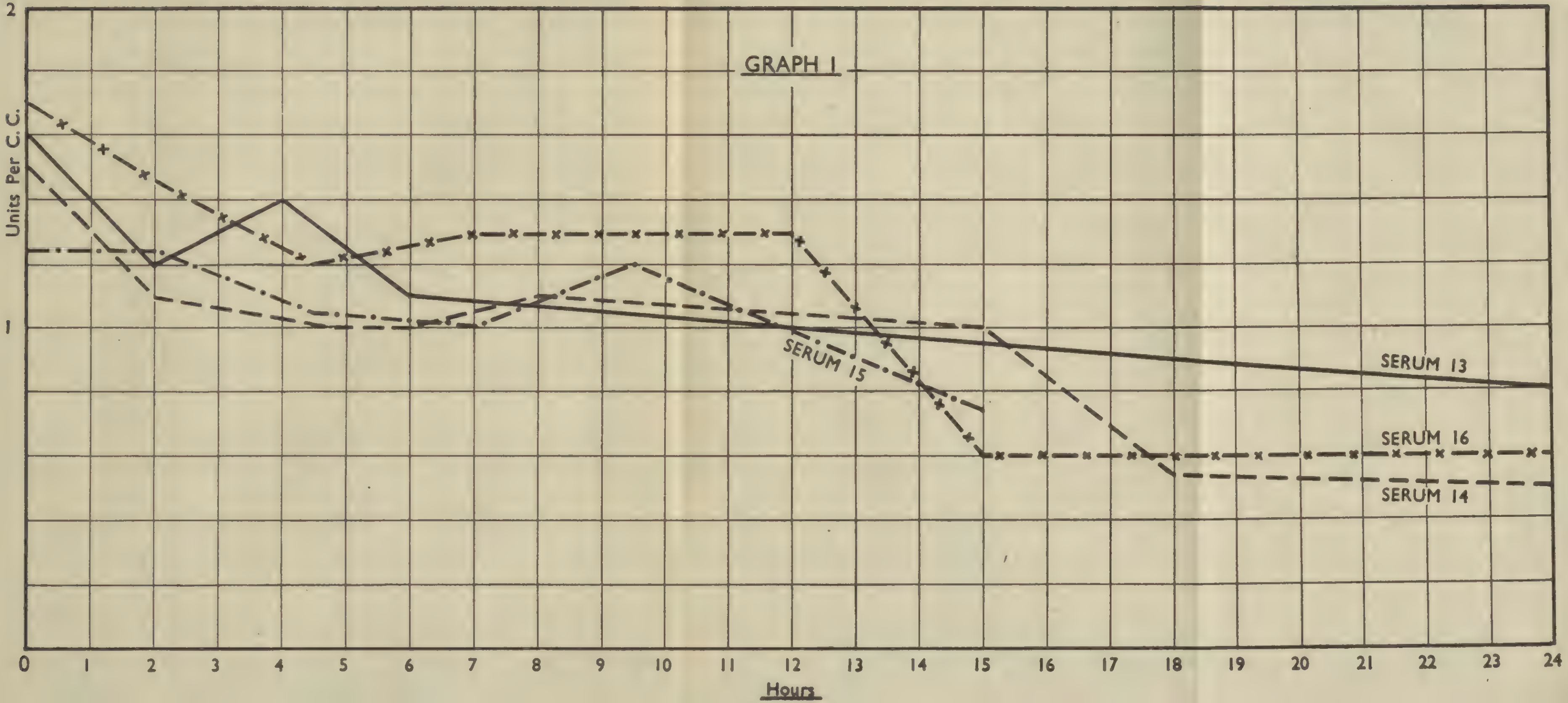
TABLE IV

Serum No.	Titre after 24 hrs at 37° C	% loss after 24 hrs at 37° C	Bacteriostatic blood levels complete
4	0.55	54	1/1
5	0.45	62	1/1
6	0.6	52	1/4
7	0.4	68	1/2
8	0.8	50	1/1
9	0.5	64	1/1
10	0	100	1/2
11	0.4	73	1/1
12	0.6	62	1/2
13	0.8	50	1/1
14	0.5	67	0
15	0.75	40	1/2
16	0.6	65	1/2
17	0.55	63	1/8 (400.000 units)
18	0.4	73	1/1

In order to ascertain whether the inactivation of penicillin by serum at 37°C. was smoothly progressive or whether an initial lag period occurred, four sera were assayed at various times during the 24 hours.

During the working day the assays were put up immediately the samples were taken, but the night samples were stored in the refrigerator until the following morning as it was considered that this would make little difference to the final results (11% in the main experiment).

The graphs show the results.


GRAPH 1
Units Per C.C.
2
1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
Hours
SERUM 13
SERUM 15
SERUM 16
SERUM 14

Graph I shows the rates of fall in titre of each of the four sera.

GRAPH I (*see folded page*)

Graph II shows the average rate of fall for all four sera and control.

GRAPH II (*see folded page*)

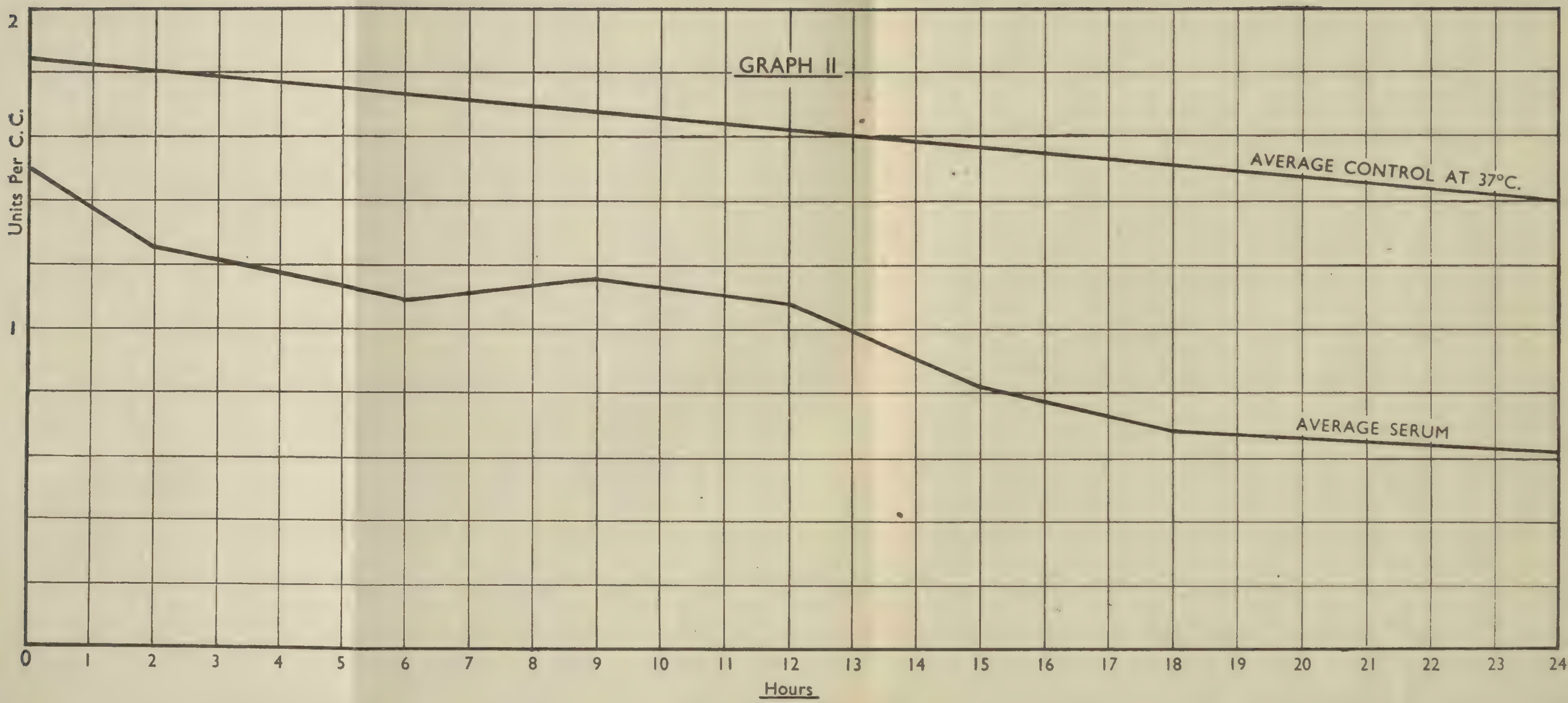
Allowing for differences due to experimental error it will be seen that the rate is smoothly progressive over 24 hours.

SUMMARY AND CONCLUSIONS

1. Human sera at 37°C has an inhibitory effect on penicillin.
2. At refrigerator temperature this effect is negligible.
3. The action is progressive from the beginning.
4. The various degrees of inhibition are not reflected in the bacteriostatic blood levels of patients undergoing drip therapy.

REFERENCES

Abraham et al (1941), Lancet, II, 177.
Bigger (1944), Lancet, Sept 23rd, 400.


GRAPH II
Units Per C.C.
2
1
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
AVERAGE CONTROL AT 37°C.
AVERAGE SERUM
Hours

THE PRODUCTION BY BACTERIA OF SUBSTANCES INACTIVATING PENICILLIN

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

In 1940 Abraham and Chain described how the crushed bodies of B. coli—an organism which is insensitive to penicillin—produced a substance which had the properties of an enzyme and which completely inactivated penicillin.

They named it penicillinase and stated further that it was not present in Staph. aureus, which is penicillin sensitive, but was to be found in M. lysodeikticus, an organism which is rather less sensitive than the staphylococcus. Later Harper (1943) described a method for producing it in reasonable quantities from a para-colon bacillus.

It was thought that a possible reason why some wounds did not react satisfactorily to penicillin therapy might be found in the presence of penicillinase-producing organisms, and that there might be a correlation between sensitivity and the production of this enzyme.

Cultures from a few wounds that had healed more slowly than the majority in a certain series showed first that the staphylococcus which was infecting them had become less sensitive to penicillin than it was originally, and second that it produced penicillinase.

A systematic examination of various organisms and staphylococci in particular was then commenced. Unfortunately, owing to pressure of other work, only a small number have been examined so far, but the results appear to be of sufficient interest to merit description.

METHOD

Sensitivity tests were carried out by the broth tube method described in the "Memorandum on Penicillin Therapy in 21 Army Group", page 63. The preparation and titration of penicillinase was by the modification of Harper's method described in the

same memorandum (pages 75-76). The table shows the organisms tested, their coagulase production if staphylococci, their sensitivity, and the weight of dried product which when suspended in sterile distilled water completely inhibited the action of 10 units of penicillin on the standard staphylococcus. The maximum weight of the dried product used in any test was 10 mgms., so that in the penicillinase production column of the table the figure "0" means that 10 mgms. failed to inhibit 10 units of penicillin and presumably therefore contained no penicillinase.

Organism	Strain	Coagulase	Sensitivity		Penicillinase production.
			Growth not inhibited by units	Growth inhibited by units	Wgt. in mgms. of dried substance inactivating 10 units penicillin
Staphylococcus	Matthews I	+	0.2	0.4	8.0
,,	Matthews II	+	0.6	0.8	0.03
,,	Addie I	+	0.04	0.06	4.0
,,	Addie	+	0.8	1.0	0.06
,,	Tourmairen I	+	2.0	4.0	0.06
,,	,, II	+	8.0	10.0	0.06
,,	Oxford H	+	0.04	0.06	0.00
,,	Hinton	—	1.0	2.0	0.00
,,	Brighty I	+	0.04	0.06	0.00
,,	Brighty II	—	0.2	0.4	0.00
,,	Perry	+	0.2	0.4	0.03
,,	Hunter	—	0.6	0.8	1.0
,,	Sachs	+	0.08	0.1	0.0
,,	Drinkall	+	0.02	0.04	0.00
Coliform	I		1000	10000	0.25
,,	II		100	1000	10.0 Trace only
,,	III		40	60	0.00
,,	IV.		0.4	0.6	0.00
p:colon	H		1000	10000	0.03
Typhosum	101		10	20	0.00
Proteus	BTU		4.0	6.0	0.00
Pyocyaneus	BTU		1000	10000	0.00
Micrococcus	Rogers		100	200	0.03

Study of this table shows that as far as the staphylococci are concerned there does not seem to be any correlation between sensitivity and penicillinase production; for example, strains Matthews I, Brighty II and Perry were all inhibited by 0.4 units

of penicillin, yet their penicillinase activity varied between none at all and so much that 0.03 mgms. inactivated 10 units of penicillin.

The gram-negative bacilli also showed no correlation between their sensitivity and the amounts of penicillinase formed.

As to the connection between wound-healing and penicillinase production all that can be said from the organisms investigated is that the micrococcus "Rogers", one of the most active penicillinase producers encountered, was found on a number of occasions in a series of wound swabs but did not appear to have any effect on wound healing, although it was lethal to mice.

On the other hand, staphylococci which both did and did not produce penicillinase were found in wounds which healed both rapidly and slowly.

It will be necessary to examine many more strains before any final conclusions can be drawn.

REFERENCES

Abraham and Chain (1940), Nature, 146, 737.
Harper (1943), Lancet, Nov. 6, 569.

THE BACTERIOSTATIC LEVELS FOUND IN THE PERIPHERAL BLOOD DURING TREATMENT BY CONTINUOUS INTRAMUSCULAR DRIP

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

In order to ascertain whether a sufficiently high concentration of penicillin was attained and maintained in the peripheral blood during routine drip therapy, a number of estimations of the bacteriostatic levels occurring at different periods during treatment were carried out.

One ampoule (nominally 100,000 units) of sodium penicillin was dissolved in 540 ccs. of sterile neutral physiological saline and given by slow drip over a period of 24 hours. Specimens of peripheral blood were taken at intervals by finger prick, and the estimations made by the method of Garrod and Heatley ("Memorandum on Penicillin Therapy in 21 Army Group", page 68).

The times the specimens were taken are reckoned from the commencement of the drip and are divided into five groups—3-6 hours, 6-12 hours, 12-18 hours, 18-24 hours, and over 24 hours up to six days.

The results are shown in the table. The degree of bacteriostasis is indicated by the dilution of the patient's serum inhibiting the growth of the "Oxford" staphylococcus.

Time group hours	Total samples	No. of samples showing bacteriostatic levels of:					
		Nil	Partial in undiluted serum	Complete in undiluted serum	Complete in serum diluted		
					$^1/_2$	$^1/_4$	$^1/_8$ or higher
3—6	18	3	1	7	2	2	3
6—12	13	1	2	5	4	1	0
12—18	21	3	1	11	2	2	2
18—24	23	4	2	8	2	1	6
24 and over	56	15	2	19	13	6	1
Totals	131	26	8	50	23	12	12
% of total		19.1	6.1	38.2	17.6	9.2	9.2

It has been suggested that an adequate bacteriostatic level has been attained if a patient's undiluted serum completely inhibits growth of the test organism. With the particular organisms employed in this series complete inhibition represents approximately 0.1 units of penicillin per cc. of serum. Unfortunately at the time these titrations were carried out the evacuation of patients from hospital was very rapid, and it was not possible to retain them long enough to correlate their clinical progress with the blood levels.

This has been done subsequently and reported in another paper* (Young et al 1945), from which it would seem that a rather higher level, 0.2 units per cc., is desirable to achieve Grade I healing of flesh wounds, but that Grade II healing may occur without a demonstratable penicillin concentration being present. A more sensitive technique would no doubt have shown the presence of a small amount of circulating penicillin.

It will be seen from the table that almost 75% of the cases showed complete bacteriostasis with diluted or undiluted serum.

* See report by Young, Evans and Hughes, page 135.

THE EFFECTS OF INDIARUBBER TUBING ON AQUEOUS SOLUTIONS OF SODIUM PENICILLIN

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

In August, 1944, a small consignment of a new type of apparatus for continuous intramuscular drip therapy was received. This was known as the "Eudrip III". The possibility was suggested that when using continuous drip apparatus the lower end of the rubber tubing might become contaminated with penicillinase-producing airborne organisms, thus leading to inactivation of the penicillin before it reached the patient.

A few experiments were carried out, therefore, to ascertain the potency and sterility of the solution at the lower end of the tube.

Two facts were immediately evident; first, that a marked fall in strength of the solution had occurred, and, secondly, that it was sterile*.

Some corroboration of this fall in potency was obtained by estimating the bacteriostatic levels attained in the blood of a small number of patients under treatment with the apparatus. With the method then available no bacteriostatic level could be demonstrated.

A comparison was made with the blood levels occurring in patients treated by continuous drip, but using either a different form of apparatus and tubing, or the Eudrip III with latex tubing; 14 out of 21 of these showed a reasonable concentration as against 0 out of 8 for the Eudrips.

* The various experiments carried out to discover the cause of the penicillin loss in the "Eudrip III" sets supplied to us are described in more detail in the August and September, 1944, Reports of the Adviser in Penicillin, 21 Army Group, and of the OC No. 3 Mob Bact. Lab. (See "Investigation of War Wounds: Penicillin", AMD/7/R. 30/44 and AMD/7/R. 34/44).

The results of these preliminary experiments are shown in Tables I, II and III. Table I shows the results obtained in the eight patients treated with Eudrip III and the original tubing as supplied with it.

TABLE I

Case No.	Days under treatment when specimens were taken	Hrs. current bottle in use	Concentration of Penicillin in units per cc.		Culture from bottom of tube	Bacteriostatic blood level
			At top of tube	At bottom of tube		
1	6	18	5400	less than 500	Sterile	Not done
2	9	18	1350	375	Sterile	0
3	8	18	Not done		Not done	0
4	1	18	2400	200	Sterile	0
5	10	18	1200	200	Sterile	0
6	2	18	2100	150	Sterile	0
7	5	15	2150	1000	Sterile	0
8	1	21	3000	500	Sterile	0

Table II shows the results obtained using the same apparatus (Eudrip III) but with latex tubing.

TABLE II

Case No.	Days under treatment when specimens were taken	Hrs. current bottle in use	Concentration of penicillin in units per cc.		Culture from bottom of tube	Bacteriostatic blood level
			At top of tube	At bottom of tube		
10	1	18	2000	2000	Not done	1/1
11	2	18	3200	2700	Sterile	0 (but needle blocked)
12	3	18	2000	1800	Not done	1/1
13	1	18	2900	2800	Not done	1/4

Table III shows the results obtained using different apparatus and tubing (modified Army Blood Transfusion Set).

TABLE III

Case No.	Days under treatment	Hours current bottle in use	Bacteriostatic blood level
15	7	2	1/2
16	1	18	1/8
17	2	23	1/1
18	8	18	0
19	1	18	1/1
20	1	18	1/2
21	1	9	1/4
22	1	9	1/2
23	1	15	0
24	4	3	0
25	1	14	0
26	2	3	1/8
27	2	3	1/1
28	1	10	1/1
29	4	15	0
30	1	7	0
31	1	10	1/1

The figures for the bacteriostatic blood levels indicate as follows:—

0 = No demonstrable bacteriostasis.

1/1 = Bacteriostasis with undiluted patient's serum only.

1/2—1/8 = Dilution of patient's serum showing complete bacteriostatis by the method employed.

In the Eudrip III the rate of flow is controlled by a capillary which allows filtered air to bubble very slowly through the penicillin solution in the reservoir bottle. It was therefore possible that some denaturation of the penicillin might be caused by this bubbling. Comparative experiments showed that the penicillin solution in the reservoir bottle slowly deteriorated, but that this was due to the effect of atmospheric temperature, and bubbling air through it made no difference to the rate of destruction. The percentage fall in potency in the reservoir was only

what experience had taught one to expect with the penicillin available at that time, and was very much less than occurred during the passage of the solution along the rubber tubing.

In view of these findings a systematic examination of all the rubber tubing available then and subsequently was carried out by the following method. Tubing as received from the suppliers was cut into 12″ lengths. One pair of 12″ lengths was used for each test. One of each pair was boiled in a strong solution of sodium carbonate for 30 minutes, washed out with running water, and finally with distilled water. The other was untreated. This was to allow for effects due to any dressing which might possibly be contained in the lumen of the tubing.

In actual fact no significant differences have been found between washed and unwashed specimens.

Two screw clamps were put on each tube, 1″ from either end, but not tightened. They were then autoclaved in a container at 20 lbs. for 20 minutes.

TABLE IV

Sample No.	Type of tubing	% loss due to effect of rubber	Suitability of tubing for penicillin administration
1	Synthetic red	93+	No
2	Natural black	46	No
3	Latex	17	Yes
4	Synthetic red	45	No
5	Synthetic red	66+	No
6	Natural red	0	Yes
7	Natural black	0	Yes
8	Synthetic red	40	No
9	Synthetic purple	56	No
10	Red, 10% natural	12	Yes
11	Red, type unknown	0	Yes
12	,, ,,	0	Yes
13	,, ,,	0	Yes
14	,, ,,	0	Yes
15	,, ,,	0	Yes
16	,, ,,	54	No
17	,, ,,	0	Yes

On cooling the tubes were filled with a solution of penicillin of known strength by means of a sterile capillary pipette and the clamps tightened. At the same time a control of the same solution was put up in a glass, screw-capped bottle. Tubes and control were replaced in the container and left at atmospheric temperature for exactly 24 hours. At the end of this period the solutions were assayed.

In all, 17 different kinds of rubber tubing have been tested by this method, with the results shown in Table IV.

The effect of the rubber tubing is shown as the percentage loss which occurred under the conditions of the experiment, when the potencies of the solutions in the tubing and in the control bottle were assayed and compared.

The table shows that the appearance of the rubber tubing has no bearing on its suitability for penicillin administration, but that each sample must be tested separately.

This has been carried out routinely in 21 Army Group since August, 1944, on all tubing supplied for use with penicillin sets.

In the method described, the effect of the rubber is more drastic than that which actually occurs in practice; consequently tubing which only shows a slight action on penicillin has been included among the samples considered suitable.

THE EFFECTS OF REACTION ON THE STABILITY OF SODIUM PENICILLIN IN GLUCOSE-SALINE AT ROOM TEMPERATURE

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

In the earlier stages of the campaign in France it was found convenient to dissolve penicillin in the standard army transfusion bottles holding 540 ccs. of glucose-saline (glucose 3.3%, saline 0.3%) for administration as a continuous intra-muscular drip.

It was occasionally found that the clinical results and bacteriostatic blood levels attained were not so good as were expected. The results were unconnected with any particular batch of penicillin, and the rubber tubing and glass ware were also found not to be at fault.

An investigation was undertaken to determine the reaction of various batches of glucose saline and other solvents.

The reactions of 7 solvents were ascertained with a quinhydrone electrode. The results are shown in Table I.

TABLE I

Solvent	Source of supply	pH
Distilled water, 100 cc. bottles	No. I B.T.U.	7.27
Distilled water, 400 cc. bottles	No. I B.T.U.	7.10
Distilled water	Canadian	7.00
Distilled water	A.B.S.D.	6.23
Normal saline	No. I B.T.U.	6.70
Normal saline	A.B.S.D.	6.23
Glucose saline	A.B.S.D.	4.63

Because of the acidity of the last named specimen it was decided to investigate the effects of glucose-saline at various pHs on sodium penicillin.

Glucose-saline (3·3% and 0·3%) was autoclaved and adjusted in a sterile manner to pHs of 4,5,6,7 and 8. This was done in two ways: by the addition of acetic acid and sodium hydroxide or by the addition of phosphate buffer.

In Table II, the reactions in experiments 1 to 3 were adjusted by the former method and 4 and 5 by the latter.

A stock solution of sodium penicillin was made in neutral distilled water so that 1cc. contained about 1000 units. This was assayed as soon as it was made.

1 cc. volumes of the stock were added to 100 cc. volumes of the various samples of glucose-saline to give a theoretical strength of about 10 units per cc. A control solution of similar strength in neutral distilled water was also made up.

All these solutions were kept at room temperature for 24 hours in order to imitate what would normally happen to a bottle of glucose-saline penicillin used as a continuous drip. At the end of the period all were assayed.

The results are shown in Table II in units per cc., and as the percentage loss of penicillin in glucose-saline when compared with the controls in distilled water. The column headed "average loss %" shows the mean percentage loss for 5 experiments at each pH.

"Original solution" is the strength of both glucose-saline and control at the beginning of the experiment.

"Control 24 hours" is the strength of the aqueous solution at the end of the experiment.

"Glucose-saline 24 hours" shows the concentrations of penicillin at the various pHs after 24 hours.

TABLE II

Experiment number		1		2		3		4		5		—
Original solution		11		12.5		10.5		6.0		14.0		--
Control 24 hours		9.5		10.0		7.5		7.0		10.0		—
		Units	%	Units	%	Units	%	Units	%	Units	%	Average loss %
Glucose-saline 24 hours	pH 4	4.0	58	3.0	70	1.8	76	4.4	38	4.0	60+	60+
	pH 5	8.5	11	4.0	60	5.4	29	7.0	0	10.0	0	20
	pH 6	6.0	37	4.5	55	7.5	0	6.0	14	8.8	12	24
	pH 7	7.5	21	8.0	20	6.0	20	6.0	14	9.6	4	16
	pH 8	7.5	21	8.0	20	6.0	20	5.1	27	10.4	0	18

The table shows that at pH 4 on an average more than 60% of the penicillin is destroyed in 24 hours at room temperature. Between pH 5 and pH 8 although the individual results fluctuate, the average losses show little differences. Further study of the table brings out some other facts.

1. The particular brand of penicillin (TRC 76) used throughout the experiments dissolved in neutral distilled water and kept at room temperature lost an average of 21% (range 14-29) in 24 hours.

2. Excluding pH 4, when the reaction of the glucose-saline was adjusted with acetic acid—sodium hyroxide, the average loss was 26%. When the adjustment was made with phosphate buffer it was only 9%.

At neutrality the loss in the buffered solution was 9% as compared with 20.5% in the non-buffered.

The indications are that a buffered solvent is more suitable than a non-buffered.

In view of these findings a special issue of approximately neutral isotonic saline without glucose was made in 21 Army Group.

All penicillin drips were made up with this solvent.

OPHTHALMIC LAMELLAE

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

A few investigations on the maintenance of bacteriostasis in the tears following the insertion of a penicillin lamella into the conjunctival sac were carried out. Each lamella contained approximately 100 units of calcium penicillin. A little smarting was felt after insertion into the normal eye but it was insignificant. The method of assay was similar to that used in serum (Memorandum on Penicillin Therapy in 21 Army Group, page 68). The dilution of the tears showing complete inhibition of growth of the test organism are shown in the table.

The tears were obtained by using a sterile capillary pipette and rubber teat.

Sample Number	Condition of eye	Bacteriostatic dilution of tears after hours		
		2	3	4
1	Normal	—	1/1	—
2	Normal	—	1/8	—
3	Conjunctivitis	—	1/8	—
4	Conjunctivitis	—	1/1	0
5	Conjunctivitis	1/4	1/2	0
6	Conjunctivitis	—	1/2	0

In all cases a reasonable level was maintained for 3 hours, although this must be dependent to some extent on the volume and rapidity of the lachrymation or discharge, and possibly on the causative organism.

STABILITY OF PENICILLIN

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

Many manufacturers of both sodium and calcium penicillin recommend that their products should be kept at cold room temperature and should be used before a certain date.

As in the field refrigeration is frequently unobtainable, a number of samples were deliberately kept at room temperature for considerable periods and then assayed to ascertain whether any drop in potency had occurred.

Similarly a number of powders and ointments containing penicillin which had been made up for the local treatment of wounds were kept under observation.

Finally a few examinations of solutions of penicillin were made on specimens kept at room temperature and in the refrigerator, and with and without the addition of merthiolate as a stabilizing agent.

All assays were carried out by the "Oxford" plate method. Owing to the difficulty of obtaining really satisfactory standards, those used came from various sources. Each was checked against its predecessor by a 16 fold assay before being taken into use and one was rechecked by the makers during the course of the experiment. This last was found to have lost some of its potency so that a correction figure has been applied to bring all the results into line.

1. *Penicillin as received from the manufacturers.*

All the specimens examined had been received 8 to 9 months earlier and had been kept in their original packings.

Table I shows the brand, batch number, expiry date or date of manufacture, the time after manufacture or expiry when the final assay was made, the stated strength of the sample and the final assay result.

TABLE I

Makers	Batch No.	Type of product	Expiry date	Date of manufacture	Time since expiry or manufacture in days or months	Stated strength units per amp. or tablet	Final assay units per ampoule or tablet
Wyeth	IC 1208	Sodium powder	18/12/44	—	121	100,000	125,000
Pfizer	1664	,,	21/12/44	—	118	100,000	200,000
Tilly	402 x 350326	,,	?	?	At least 9 months since manufacture	100,000	200,000
Merck	262	,,	24/11/44	—	145	100,000	200,000
Commercial Solvents	44050501	,,	6/11/44	—	163	100,000	200,000
Squibb	974080	,,	26/10/44	—	174	100,000	200,000
T. R. C.	56	Sodium tablet	—	13/4/44	370	6,000	6,250
T. R. C.	67	,,	—	May 44	11 months	8,250	5,000
T. R. C.	75	,,	—	June 44	10 months	7,500	1,200
Imperial Chemicals	27HP 8004	Calcium tablet	—	June 44	10 months	6,500	6,250
,,	28HP 8005	,,	—	June 44	10 months	7,500	10,000
,,	29HP 8006	,,	—	July 44	8 months	8,000	11,700

It will be noted that all the American products have an assay value higher than that stated on the label. This has been a consistent feature among the early batches throughout the campaign in NW Europe, no matter what standard was used. The reason is not known but it may be due to different methods of assay and standardization in the USA. What is obvious is that the powders have all kept satisfactorily in spite of not being refrigerated.

The tablets have been variable, some keeping extremely well and others deteriorating.

2. *Penicillin in "Sulpha" and other powders.*

Powders containing calcium penicillin for the local treatment of wounds were received from time to time from the manufacturers or made up by No. 3 Mobile Bact. Lab. They were stored at room temperature. Assays were carried out on receipt or manufacture and periodically later. The results are shown in Table II.

TABLE II

Makers	Vehicle	Original Titre	Interval days	Final Titre	Remarks
3 MBL	Sulphanilamide	4400	231	5200	
3 MBL	Marfanil Prontalbin	6000	161	6000	
Boots	Sulphathiazole proflavine (1%)	4800	222	2500	Fell to 3700 in 7 days and 3200 in 39 days
3 MBL	Nuflav (Sulphathiazole proflavine 2%)	4200	232	3600	
ICI	Microcrystalline Sulphamezathine	5000	53	4000	
3 MBL	Dried plasma	4800	119	4800	
3 MBL	Dried plasma Denatured	4000	119	4200	Denatured by heating to 60°C for 30 minutes
3 MBL	Lycopodium	6400	27	6400	Insufflates badly, not pursued

It will be seen that powders containing sulphathiazole and proflavine have deteriorated to a greater degree than the others. The rate of fall will, of course, vary with the particular batch of penicillin used.

More recent batches which are purer should keep better.

3. *Penicillin solutions.*

In the early days of penicillin therapy it was always recommended that solutions of penicillin for injection should be stored in the refrigerator and not used after 24 hours.

At the request of the Adviser in Dermatology, 21 Army Group, a solution of Sodium Penicillin was made up in 1 in 1000 aqueous merthiolate for external use in dermatological cases.

The opportunity was taken to compare the stability of this with an ordinary aqueous solution of penicillin.

METHOD

Sodium penicillin TRC 76 10,000 units per tablet was used. One tablet was dissolved in 20 ccs. sterile distilled water and a second in 20 ccs. of the merthiolate solution. Each solution was assayed immediately; the aqueous having a titre of 500 units per cc. and the merthiolate 750 units per cc.

It had previously been ascertained that the addition of 1 in 1000 merthiolate to penicillin solution of this strength made no appreciable difference to the ring of inhibition produced on a staphylococcal test plate.

Each solution was divided into two equal parts, one part being kept in the refrigerator and the other at room temperature. Assays of all four were made at intervals with the results shown in table III.

As the original stock solutions were not of equal strength the table shows the subsequent assay titres as percentage of the original stock solutions.

TABLE III

Days since made	REFRIGERATOR		ROOM TEMPERATURE	
	Aqueous solution %	Merthiolate solution %	Aqueous solution %	Merthiolate solution %
0	100	100	100	100
4	90	60	100	67
7	100	80	120	73
14	105	88	80	53
28	100	80	70	47
63	100	67	80	30
90	100	57	58	16

The table shows that merthiolate did not increase the stability of this sample of penicillin; also that the aqueous solution retained 100% of its potency after three months in the refrigerator and for about seven days at room temperature.

4. *Penicillin in Lanette Ointment.*

The lanette ointment used was a sample emulsion of 30% lanette wax SX in water. It was sterilised in the autoclave and the requisite amount of calcium penicillin dissolved in a few cc. sterile water added while the ointment was still warm.

The concentration used was 500 units per gramme of ointment. It was stored at room temperature. The method of assay was a comparative one, assay cylinders being filled with the mixture and stood on plates of medium already inoculated with the standard staphylococcus. A control cylinder was also put on and filled with an aqueous solution containing 500 units per cc. The diameter of the rings of inhibition after incubation were compared. The diameter of that produced by the ointment is shown as a percentage of the control ring (Table IV).

TABLE IV

Days since made	Diameters of inhibitory rings in m. m.		Lanette % of control
	Lanette	Control	
0	40	42	95
1	43	44	98
3	38	42	90
7	34	42	81
14	34	38	89
28	35	40	87
56	26	37	70
83	26	38	68

In 83 days a fall of 28% had occurred in the concentration of the penicillin. As long as this was remembered it could still be used therapeutically.

Finally a similar ointment was made, but using non-injectable sodium penicillin. This was put in a small cardboard ointment container and carried about, loosely wrapped in cellophane, in the trouser pocket, the idea being to ascertain whether the mixture would be sufficiently stable to give to dermatological out-patients. An assay was not carried out immediately, the first being done 5 days after manufacture.

The results are shown in Table V.

TABLE V

Days since made	Diameters of inhibitory rings in mm.		Lanette % of control
	Lanette	Control	
5	32	38	84
6	27	36	75
11	27	37	73
15	27	39	69

It would appear that the ointment is sufficiently stable under these conditions to be used clinically for about a week.

PENICILLIN IN SYNOVIAL AND PERITONEAL FLUIDS

By Maj. K. E. A. Hughes, RAMC, OC No. 3 Mobile Bacteriological Laboratory

It has been stated that when penicillin is given parenterally it has difficulty in passing the serous membrane barriers of the joints and peritoneal cavity, and consequently the concentrations achieved in the synovial and peritoneal fluids are insufficient to produce bacteriostasis of an infecting organism. Whether this is true of normal synovial and peritoneal membranes is unknown, but it is certainly untrue of those which are inflamed, although the concentration is often lower than in the blood.

Parenteral penicillin (100,000 units in 540 cc. of saline) was given by continuous intramuscular drip to a small number of patients, and the synovial fluid obtained by aspiration, or the peritoneal fluid issuing from a drainage tube, was examined. Simultaneous specimens of blood were also examined.

The method used for the estimation of bacteriostatic activity in the end was similar to that used for the blood serum ("Memorandum on Penicillin Therapy in 21 Army Group," page 68). The results are shown in the table. "Drip time" is the period that the drip had been running before the specimens were taken.

The table shows that 6 out of 7 synovial and 3 out of 4 peritoneal fluids contained adequate amounts of penicillin. In case 6, the apparently higher level in the joint fluid is probably due to the experimental error of the technique employed.

In case 10, there was an abundant growth of a coliform bacillus, and no penicillin was demonstrable in the peritoneal fluid. This organism, which grew freely in broth containing 1000 units of penicillin per cc., was inhibited by 10,000 units, and was found to produce considerable quantities of penicillinase, 0.3 mg. of the acetone-ether treated organism inactivating 10 units of penicillin.

Sample No.	Source of fluid	Type of fluid	Culture of fluid	Drip time in hours	Bacteriostatic dilutions found in: Blood serum	Fluid
1	Knee joint	Slightly blood stained. No pus	Sterile	20	1/2	1/1
2	Knee joint	Straw-coloured. No blood or pus	Sterile	20	1/2	1/1
3	Knee joint	Straw-coloured. Clot ++ No pus or blood	Sterile	20	1/1	1/1
4	Knee joint	Straw-coloured. No pus or blood	Sterile	12	1/1	0
5	Knee joint	Purulent. No blood	Diphtheroids Scanty growth	48	1/8	1/1
6	Knee joint	Straw-coloured. Clot + No pus or blood	Sterile	16	1/1	1/2
7	Knee joint	Slightly bloodstained. No pus	Sterile	36	1/4	1/1
8	Peritoneum: perforated duodenal ulcer	Clear yellow	Sterile	14 19	1/8 1/8	1/2 1/2
9	Peritoneum: appendix abscess	Slightly purulent	B. Coliformis Scanty growth	$1^1/_2$ 15	1/1 1/2	0 1/1
10	Peritoneum: appendix abscess	Purulent	B. Coliformis abundant growth St. anhaemo. Scanty growth	30	1/8	0
11	Peritoneum: appendix abscess	Purulent	Staphylococci	12	1/1	1/1

THE PASSAGE OF PENICILLIN THROUGH SYNOVIAL MEMBRANE

By Maj. J. G. Bonnin, RAMC, Orthopaedic Specialist, and Maj. A. P. Prior, RAMC. Pathologist

The object of the investigation was primarily to ascertain whether penicillin administered parenterally could pass through the synovial membrane and be detected in the synovial fluid.

TECHNIQUE EMPLOYED TO DEMONSTRATE PRESENCE OF PENICILLIN

Agar plates were seeded with a young culture of the Oxford staphlycoccus and dried. Using a No. 5 cork borer punch holes were made in the medium and the discs removed.

Appropriate dilutions of the samples to be tested were made with neutral saline, and two drops were placed in each punch hole, using a Pasteur pipette. All assays were done in duplicate, and the same pipette was used throughout in order that the volumes of all the samples should be the same. After incubation overnight the diameters of the rings of inhibition produced were measured.

PENICILLIN ADMINISTERED PARENTERALLY

1. In the first three cases investigated 20,000 units penicillin were given intramuscularly, and one hour later samples of the blood serum and synovial fluid were obtained for testing.

The blood sera all showed a small degree of inhibitory activity, but no penicillin was detected in the synovial fluid.

2. In the second series of three cases the dose of penicillin was increased to 40,000 units, and the interval before taking the samples was reduced to 30 minutes.

In all three a dilution of 1 in 4 of the serum showed good inhibitory activity, but only traces of penicillin were present in the synovial fluid.

3. The third series consisted of six cases. The dose of penicillin used was 80,000 units, and samples were taken 30 minutes after intramuscular administration. All sera showed the presence of penicillin, in some cases even when diluted to 1 in 16.

In one case no penicillin was detected in the synovial fluid in spite of the fact that his serum was bacteriostatic when diluted 1 in 8.

In a second case the serum diluted 1 in 8 gave a ring of inhibition 12 mm. in diameter; while the synovial fluid diluted 1 in 4 gave a ring of 20 mm.

The four remaining synovial fluids were all bacteriostatic when diluted 1 in 2.

These findings show that penicillin if given parenterally in sufficient dosage does in fact penetrate the synovial membrane. Blood-stained fluids were avoided in the experiment to obviate the possibility of penicillin being conveyed directly to the joint cavity in the blood.

PENICILLIN INJECTED LOCALLY

One case of hæmarthrosis was used to ascertain how long penicillin would persist in the synovial fluid when injected directly into the joint cavity; 100,000 units were given and aspirations performed at 24, 48 and 72 hours.

Penicillin was present in the first two samples, but was not detected at 72 hours.

At 48 hours the joint fluid when diluted 1 in 16 gave a zone of inhibition 12.5 mm. in diameter.

CONCLUSION

Penicillin can penetrate the synovial barrier, but the concentration in the synovial fluid is less than in the serum.

CASE ILLUSTRATING PASSAGE OF PARENTERAL PENICILLIN INTO JOINT

By Lt.-Col. A. G. R. Lowdon, RAMC, Officer i/c Surgical Division, No. 6 (Br.) General Hospital

The following case report is given in some detail as it shows that an effective concentration of penicillin was obtained in a knee joint by parenteral administration only, in a case in which a fracture of the femur involved the joint.

6394308 BSM AGATE, C. H.—RA 109 LAA Regt.

Diagnosis: S.W. Pen. Knee Rt., Involving Joint.

History: Wounded 23 December, 1944, in right popliteal area. Operation same day by Major Aylett at 10 CCS. "Debridement of wound, K.J. found open. Femoral condyles penetrated and disrupted by large F.B. F.B. removed. One stitch in post capsule. Extension in Tobruk P.O.P."

On admission to No. 6 (Br.) General Hospital on 24 December, 1944, he was "travel tired" and rather toxic. Hb. 65%. There was no evidence of damage to a major vessel or nerve. X-rays showed a comminuted fracture of lower end of femur extending vertically into the knee joint and with only slight displacement. The wound in the popliteal region was septic and there was some effusion into the joint. On 27 December, 1944, aspiration of the joint produced 20 cc. blood stained fluid which was sterile on culture.

There was no note in his records that he had received penicillin either locally, into the joint or parenterally. He certainly received no penicillin locally or parenterally from 24-27 December.

On 28 December an intramuscular penicillin drip was started at 1900 hours and was continued at a regular rate for five days with dosage of 100,000 units per 24 hours.

At 1000 hours on 30 December (*i.e.* 39 hours after commencement of penicillin drip) specimens of blood serum and knee joint fluid were taken: both showed an effective concentration of penicillin; both were bacteriostatic in a dilution of 1 in 4 to the Oxford Staph. The knee joint fluid was again sterile.

PENICILLIN CONTENT OF BODY FLUIDS IN PENICILLINISED PATIENTS

By Lt.-Col. F. N. Foster, RAMC, Officer i/c Surgical Division, and Capt. J. Colquhoun, RAMC, Pathologist, 105 (Br.) General Hospital

As there was much doubt whether or not penicillin reached the serous cavities of the body when a patient was on parenteral penicillin, we decided to estimate the fluid from such cavities for their penicillin content.

As most cases were operative emergencies, we felt that using a continuous intramuscular drip there would not be sufficient time to penicillinise the patient before withdrawing the fluid, and so normally we gave an initial dose of 50,000 Oxford units penicillin, followed by 15,000 units three-hourly.

The penicillin used was assayed and found to be as stated on each ampoule, *i.e.* 100,000 units. The penicillin levels of the blood and fluids were estimated by the slide-cell technique, using the modified slide cell described by Bigger, Thomas and Caldwell, and the Oxford staphylococcus. It is assumed that where the growth of the Oxford staphylococcus is just inhibited in the serum that serum contains 1/16 Oxford unit per cc.

Knee Joint

As can be seen in Table I, penicillin can be demonstrated in the knee joint whether the swelling of the joint is stationary or tending to decrease. As we felt that only those cases which required surgical interference should be investigated, considering it unjustifiable to interfere with knee joints purely to estimate their penicillin content, only pathological conditions are recorded.

When continuous intramuscular drip therapy is used, as it was in eight cases, the penicillin content of the fluid is much the same as that of the blood.

TABLE I *KNEE JOINTS*

I. Penicillin being administered by continuous intramuscular drip.

Patient	Disease	Equivalent 24 hr. consumption of penicillin (Oxford units)	Blood penicillin level 3-4 hrs. after starting drip (Oxford units/cc.)	Blood and Fluid penicillin levels 6-7 hrs. after start of drip (Oxford units/cc.) Blood	Fluid	Remarks
3	Traumatic Synovitis	250,000	6/32	6/32	6/32	Swelling tending to decrease.
4	do	150,000	4/32	4/32	4/32	Swelling stationary.
5	do	100,000	4/32	2/32	2/32	Swelling tending to decrease.
6	do	60,000	1/32	0	3/32	Swelling stationary. Drip at rate of about 100,000 units/cc. for first 2½-3 hrs, then much reduced.
10	do	400,000	—	8/32	4/32	Swelling tending to decrease.

The synovial fluids in the above cases were all sticky straw coloured clotted fluids, containing no blood and being sterile on culture.

Patient	Disease	Equivalent 24 hr. consumption of penicillin (Oxford units)	Blood penicillin level 3-4 hrs. after starting drip (Oxford units/cc.)	Blood	Fluid	Remarks
1	Traumatic haemarthrosis	500,000	8/32	—	—	Surgical interference not warranted.
2	do	700,000	12/32	16/32	6/32	Swelling stationary.
9	do	235,000	4/32	3/32	4/32	Swelling stationary.

These fluids from the knee were much like blood, being sterile on culture.

II. Penicillin administered by 3 hourly intramuscular injections of 15,000 units.

Patient	Disease	Time after routine 15,000 units per injection	Blood penicillin level (Oxford units/cc.)	Fluid penicillin level (Oxford units/cc.)	Remarks
7	Traumatic synovitis	22 hours	NIL	NIL	Swelling stationary.
8	Traumatic haemarthrosis	2½ hours	NIL	3/32	do

Both fluids were sticky, straw-coloured, clotted and blood free and were sterile on culture.

TABLE II — PLEURAL FLUIDS

Patient	Disease	Time after routine injection fluid and blood taken	Units of penicillin/cc. fluid	Units penicillin/cc. blood	Remarks
1 (a)	G. S. W. Chest with	1 hour	3/32	—	Fluid from chest = blood and was sterile.
1 (b)	Haemothorax	1½ hour	2/32	3/32	

Patient was given 50,000 units penicillin statim and thereafter 30,000 units 3 hrly, intramuscularly.

Patient	Disease	Time after routine injection fluid and blood taken	Units of penicillin/cc. fluid	Units penicillin/cc. blood	Remarks
2 (a)	Fractured ribs with traumatic pleural effusion	2 hrs. after initial injection of 50,000 units penicillin	3/32	3/32	Fluid straw-coloured, clotted, free from blood, sterile.
2 (b)	do	1 hour after injection of 15,000 units penicillin	6/32	8/32	

Patient was given initial injection of 50,000 units penicillin and 3 hours later one of 15,000 units

Here also, whether the fluid was blood stained or not, penicillin was found therein. No local instillation of penicillin was given in these cases.

TABLE III *HYDROCELE*

Penicillin was administered by continuous intramuscular drip.

Equivalent 24 hour consumption of penicillin (Oxford units)	Blood penicillin level 3 hrs. after start of drip (units/cc.)	Fluid and blood penicillin levels 6 hrs. after start of drip (units/cc.)		Remarks
		Blood	Fluid	
200,000	3/32	4/32	3/32	Swelling stationary

The fluid was blood free and sterile on culture.

In the one case investigated penicillin was found in the fluid.

TABLE IV *AMOEBIC ABSCESS OF LIVER*

50,000 units penicillin were administered intramuscularly 2 hours before the abscess was drained.

Penicillin content of the fluid was 2/32 units/cc.

The fluid from the abscess was typical of an amoebic abscess and was sterile on culture.

In the one case investigated penicillin was found in the fluid.

TABLE V — *PERITONEAL FLUID*

Penicillin was administered by 3 hourly injections of 15,000 units intramuscularly with an initial dose of 50,000 units.

Patient	Disease	Time blood and peritoneal fluid taken	Penicillin level in units/cc. Blood	Fluid	Remarks
2	G. S. W. abdomen	$2\frac{3}{4}$ hrs after the 50,000 unit injection	2/32	3/32	
3	G. S. W. abdomen	2 hrs after first injection of 15,000 units	4/32	4/32	Patient was oliguric
5	Abdominal crush injury	$2\frac{1}{2}$ hrs after first inject. of 15,000 units	6/32	4/32	Patient was oliguric
In the above cases the peritoneal fluid was sterile and contained much blood.					
1	Acute intestinal obstruction	1 hr after first injection of 15,000 units	—	12/32	Fluid blood-free and sterile
7	T. B. effusion	$1\frac{1}{4}$ hrs after single inject. of 100,000 units	32/32	6/32	Fluid was clear, straw-coloured, blood-free and sterile, there being 3-4 pints of it.
4	Acute appendicitis	$2\frac{1}{4}$ hrs after first inject. of 15,000 units	8/32	8/32	Fluid was cloudy, pale yellow, blood-free, sterile, but contained many pus cells and peritoneal epithelial cells
6	Perforated appendix	1 hr after injection of 50,000 units	12/32	8/32	

In case 6 the fluid was turbid and brownish, containing some blood. Direct films showed many pus cells and a heavy mixed infection and/or contamination with gram +ve and —ve bacilli, gram +ve cocci and a streptothrix.

Aerobic culture yielded a pure growth of a B. Coli, whilst anaerobic culture yielded a heavy mixed growth, including an anaerobic streptococcus and large gram +ve bacilli often in pairs. This B. Coli. did not produce a penicillinase. Unfortunately there was neither time nor facilities to investigate further the other organisms isolated.

Comment: As with the fluid in the other serous cavities, penicillin was found in the peritoneal fluid whether or not blood was also present.

Case 7 is interesting because although the peritoneum contained at least 3-4 pints, if not as much as 6 pints, of fluid, penicillin was found there in a therapeutic quantity.

Case 6 is instructive in that penicillin was found in the pus despite its containing many varying organisms.

CEREBRO-SPINAL FLUID

Four normal patients were given an intramuscular injection of 50,000 units penicillin, followed by 15,000 units three hours later, and samples of their blood and cerebro-spinal fluid removed one hour after the second injection and their penicillin content estimated.

In none of these patients could the presence of penicillin be demonstrated in the cerebro-spinal fluid, although the penicillin level in the blood was as would be expected. With normal methods of administration and dosage, penicillin was therefore not detected in the cerebro-spinal fluid. There are, however, important differences between the cases used for investigating the spinal membranes and those of the other serous cavities.

1. The spinal cases were all normal, whereas in the case of the other serous cavities a pathological process was present.

2. As compared with other cavities, the cerebro-spinal secretory surface is small.

3. The cerebro-spinal space is closed and of relatively small capacity, and the normal positive fluid pressure is easily increased inside the rigid boundaries. By comparison the pleural and peritoneal cavities have larger capacities and secretory surfaces, expandible walls, and negative phases of pressure within. The conditions existing in the cerebro-spinal space therefore tend to retard the free effusion of fluid and the passage of penicillin.

SUMMARY

The results of these investigations show that, with the possible exception of the meninges, penicillin is capable of passing serous and synovial barriers in therapeutic concentrations in patients undergoing parenteral penicillin therapy.

To demonstrate penicillin secretion into the cerebro-spinal fluid either cases with pathological conditions of the meninges will have to be used, or a much modified technique of investigation employed.

We should like to thank our colleagues in the Surgical Division, both medical and nursing, for their help in this investigation, and also the laboratory staff.

STUDY OF THE BACTERIOSTATIC POWER OF SYNOVIAL FLUID DURING PARENTERAL PENICILLIN TREATMENT

By Lt.-Col. F. A. Simmonds, RAMC, Officer i/c Surgical Division, 113 (Br.) General Hospital, Maj. T. P. N. Jenkins, RAMC, Orthopaedic Specialist, and Maj. R. D. Mackenzie, RAMC, Pathologist

Penicillin was given parenterally for 24 hours prior to aspiration to alternate cases of traumatic synovitis. The dosage was 100,000 units by continuous intra-muscular drip, or 160,000 units by three-hourly interrupted doses.

The specimens sent for examination were:—

(*a*) Blood taken from the vein before commencing penicillin.

(*b*) Blood taken from the vein at the termination of 24 hours dosage with penicillin.

(*c*) Synovial fluid aspirated from the knee joint at the termination of 24 hours dosage with penicillin.

(*d*) In one case only was the joint aspirated before giving penicillin. In other cases it was not considered a justifiable procedure.

Alternate cases were given no penicillin. Case 2 is included in the series although 16 grammes of sulphathiazole were given during the 24 hours preceding aspiration. Only very slight but equal inhibition was registered in the blood and synovial fluid in this case.

The estimations were carried out by Major R. D. McKenzie who compared the inhibitory action on the growth of the Oxford Staphylococcus of blood and synovial fluid at dilutions of 1/1, 1/2, 1/4, 1/8 and 1/16.

The extent of the growth was estimated and the results for each case were recorded in tables in which:—

o = no growth (total inhibition).
+ = slight growth (slight inhibition).
+ + = moderate growth (partial inhibition).
+ + + = profuse growth (no inhibition).

For example. Case I.

	Dilution				
	1/1	1/2	1/4	1/8	1/16
Blood before administration of penicillin	+	++	+++	+++	+++
Blood after administration of penicillin	O	O	O	++	+++
Synovial fluid before administration of penicillin	++	+++	+++	+++	+++
Synovial fluid after administration of penicillin	O	O	+	++	+++

From the series of cases four groups of results were available:—

(*a*) Blood, no penicillin given.

(*b*) Blood, penicillin given.

(*c*) Synovial fluid, no penicillin given.

(*d*) Synovial fluid, penicillin given.

In order to facilitate comparison of the groups, the mean result of each group was obtained. For the symbols o, +, ++, +++, the numbers o, 1, 2, 3, were substituted respectively. The numbers in the column under each dilution were added together and the total was divided by the number of cases in the group. The result obtained is the mean result of the group.

Table I. *Blood; no penicillin given.*

	1/1	1/2	1/4
Case 1	1	2	3
Case 2	1	2	3
Case 5	1	3	3
Case 8	1	3	3
Case 4	1	2	3
Case 6	2	3	3
Case 7	1	3	3
Case 9	1	2	3
Case 10	1	2	3
Total Cases 9	10	22	27
Mean result	1.1	2.4	3

Table 2. Blood after administration of penicillin.

	1/1	1/2	1/4
Case 1. 26/12	0	0	0
Case 3	0	2	3
Case 5	0	1	3
Case 8	0	0	0
Case 11	1	2	3
Case 12	1	3	3
Total Cases 6	2	8	12
Mean result	0.3	1.3	2

Table 3. Synovial Fluid; no penicillin given to patients.

	1/1	1/2	1/4
Case 1. 22/12	2	3	3
Case 4	0	1	3
Case 6	2	3	3
Case 7	1	2	3
Case 9	1	2	3
Case 10	0	2	3
Total Cases 6	6	13	18
Mean result	1	2.1	3

Table 4. Synovial Fluid taken following administration of parenteral penicillin.

	1/1	1/2	1/4
Case 1. 26/12	0	0	1
Case 3	0	2	3
Case 5	0	0	1
Case 6	0	1	1
Case 11	0	2	3
Case 12	0	2	3
Total Cases 6	0	7	12
Mean result	0	1.2	2

Summary of mean results.

Groups	Dilution		
	1/1	1/2	1/4
Blood: no penicillin	1.1	2.4	3
Blood: parenteral penicillin given	0.3	1.3	2
Synovial fluid; no penicillin	1	2.1	3
Synovial fluid; parenteral penicillin given	0	1.2	2

o = Complete inhibition.
3 = No inhibition.

CONCLUSION

The conclusion cannot be definite from any small series of cases, yet the results are suggestive.

(*a*) Comparing the bacteriostatic power of blood and synovial fluid in which there had been no penicillin therapy:—

Groups	1/1		1/4
Blood: no penicillin	1.1	2.4	3
Synovial fluid; no penicillin	1	2.1	3

There is a suggestion that synovial fluid in traumatic arthritis is more bacteriostatic than the patient's own blood.

(*b*) In this series, the relatively incomplete inhibition of growth shown by the blood in the group to which penicillin had been given may be due to several factors.

Groups	1/1	1/2	1/4
Blood: no penicillin	1.1	2.4	3
Blood: penicillin given	0.3	1.3	2

(i) Three patients were given intra-muscular injections at 3-hourly intervals—Cases 1, 2, 12—and owing to pressure of work we have no note of the time factor between the last dose of penicillin and the collection of the specimen.

(ii) The remaining patients were given continuous intramuscular penicillin drips and we suggest that the poor inhibitory value of the blood was due to the high temperature at which the wards were maintained—approximately 20 deg. Centigrade.

(*c*) Comparing the bacteriostatic power of synovial fluid during penicillin therapy with synovial fluid in which penicillin had not been given.

Groups	1/1	1/2	1/4
Synovial fluid; no penicillin given	1	2.1	3
Synovial fluid; parenteral penicillin given	0	1.2	2

The bacteriostatic power of synovial fluid is increased by penicillin therapy. This increase is equivalent to a dilution of 1/2 and is therefore an increase in power of approximately 100%.

(*d*) Comparison of the bacteriostatic power of blood and synovial fluid when penicillin is given.

Groups	1/1	1/2	1/4
Blood: parenteral penicillin given	0.3	1.3	2
Synovial fluid; parenteral penicillin given	0	1.2	2

This suggests that the bacteriostatic power of the synovial fluid approximates that of the patient's blood. This is tentative evidence that penicillin enters the synovial fluid from the blood. It is noted, however, that the level of blood bacteriostatic power reached is lower than is usually expected.

SUMMARY

The evidence suggests that:—

(*a*) The bacteriostatic power of synovial fluid is increased by parenteral penicillin therapy.

(*b*) The synovial bacteriostatic power follows that of the patient's blood when penicillin is given.

LOCAL ANÆSTHETICS AND PENICILLIN THERAPY

By Maj. F. F. Rundle, RAMC, Surgical Specialist, No. 23 (Scottish) General Hospital

Superficial wounds, notably those of the scalp, are often cleansed and sutured after infiltrating the surrounding tissues with local anæsthetic agent. When freeing the skin flaps, injected fluid inevitably escapes into the wound. What effect has this upon insufflated penicillin?

A further problem in penicillin therapy is the pain of repeated injections. Administration by continuous drip does not always provide a solution. Can some long-acting analgesic agent be efficiently combined with penicillin to render serial injections painless?

METHOD

The anæsthetic solution to be tested has been added to a penicillin solution of known strength and the activity of the mixture (test solution) compared with that of the same penicillin solution with distilled water added (control solution). The Oxford assay method has been used. A cylinder implanted on a nutrient agar plate, seeded with staphylococci, is filled with test solution, and after incubation the zone of inhibition is measured and compared with that round a control cylinder. In practice a solution of sodium penicillin, 10 units/cc., has been added to an equal volume of the test agent at double strength. Thus, in the mixture, penicillin, 5 units/cc., is exposed to the concentration of anæsthetic agent in common use.

The penicillin content of the test solution is assayed immediately after mixing (0 hours) and subsequently at 1, 2, 4 and 8 hours. In the intervals, control and test solutions are incubated at 38°C. A control cylinder is included on each plate and anti-bacterial activity by the test agent itself is excluded

by filling one cylinder with its solution at usual strength. Each experiment included an assay plate relating known dilutions of the penicillin solution (5, 3.5, 2, 1 and 0.5 units/cc.) to widths of inhibited zone.

FIGURE I

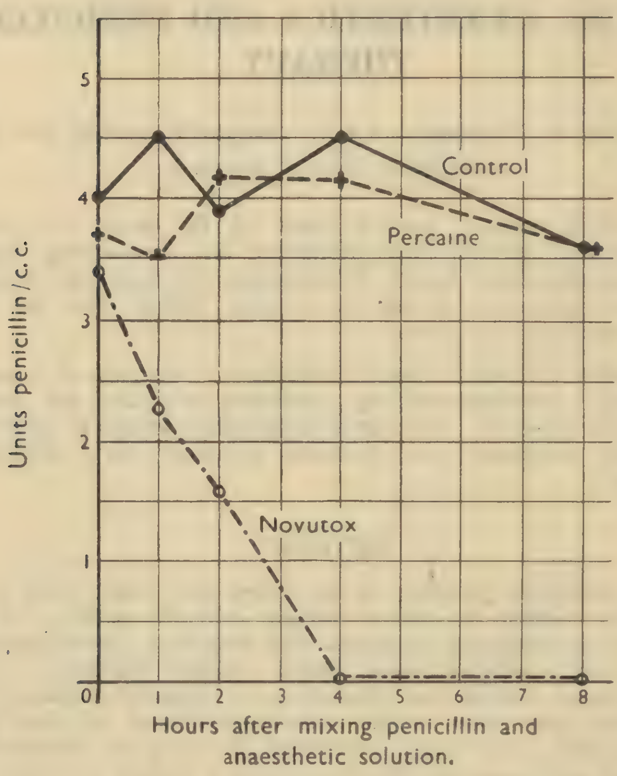


Fig. 1.

Curves showing penicillin content of control, percaine and Novutox solutions incubated at body temperature for 8 hours.

Control: Distilled water + penicillin, 10 units/cc. in equal parts.

Percaine: Percaine 1:1500 + penicillin, 10 units/cc. in equal parts.

Novutox: Novutox (2% procaine) + penicillin, 10 units/cc. in equal parts.

Penicillin decay curves: Typical curves for the control, percaine and "Novutox" mixtures are shown in Fig. 1. At the end of eight hours in the incubator the control solution regularly loses some activity (an average, in 12 assays, of 25% of its theoretical initial value, 5 units/cc.). With percaine 1:3000 present in solution, the loss is not significantly greater. "Novutox", present in half-strength, destroys penicillin completely after four hours.

By adding the deficits of 0, 1, 2, 4, and 8 hours and expressing the sum as a percentage of the total penicillin content in the control cylinders, we obtain an index of inactivation over the whole period of exposure thus:—

		Hours after mixture				
		0	1	2	4	8
Penicillin content units/cc.,	Control mixture	4.0	4.5	3.9	4.5	3.6
	"Novutox" mixture	3.4	2.3	1.6	0	0
	Deficits	0.6	2.2	2.3	4.5	3.6

Total deficit = 13.2 Percentage inactivation = 64.

The inactivation produced by other agents is as follows:—

1:3000 decicain in mixture	1 per cent*
1:3000 percaine in mixture	7 per cent
2% procaine hydrochloride in mixture	22 per cent
1% cocaine hydrochloride in mixture	25 per cent.

(Average results in 3 experiments.)

Adrenaline: As is well known, admixture of adrenaline prolongs the action of local analgesics. A concentration of 1:250,000 is advised with procaine, but with percaine and decicain 1:500,000 appears to be adequate. Penicillin, 5 units/cc., has been exposed to increasing dilutions of adrenaline hydrochloride (BP) and assays done as with the analgesic agents themselves. The results are shown in Fig. 2 in which percentage inactivation is plotted against the log of dilution. The decline in inactivation appears to be described by a straight line which cuts the abscissa at a dilution of adrenaline with log of approximately 5.3. We may conclude that at dilutions of 1:200,000 or greater there is no significant loss of penicillin in the mixture, and that the use of adrenaline in its usual strength for local infiltration is harmless.

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* Decicain (Anethaine) has been supplied by the manufactures for field trials. The other agents are those in general army supply.

FIGURE II

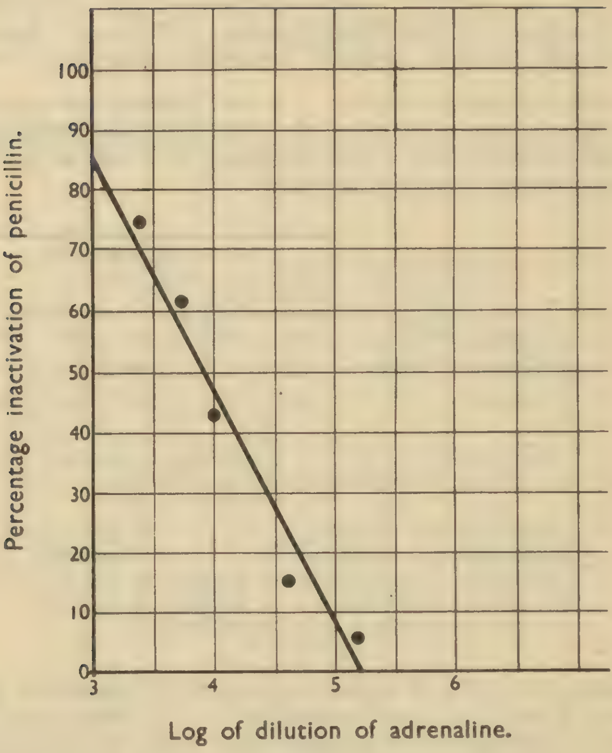

Fig. 2.

Inactivation of sodium penicillin, 5 units/cc., exposed to dilutions of adrenaline hydrochloride (BP). Each point gives the average result obtained in 3 experiments.

Relation to conditions in the wound: Exposure of penicillin to test agent has been maintained at body temperature over an eight-hour period. It is likely that appreciable amounts of anæsthetic fluid remain in the wound for this period.

A low concentration of penicillin, 5 units/cc., has been used. It is thus assured that any destruction of penicillin is evident; with higher concentrations the relative widening of the zone of inhibition decreases markedly and some destruction might be missed.

Since the general bacterial titre of penicillin is less than 1 unit/cc. most of our range is above that required therapeutically. It may, however, be of the same order as that in wound fluid after insufflation.

Inactivation of penicillin by local anæsthetics and adrenaline is correlated with the pH of the mixture. Thus the pH of both "Novutox" and adrenaline hydrochloride (BP), which markedly inactivate penicillin, is approximately three, whereas percaine and decicain, which do not, have solutions which are neutral or only very faintly acid. With the more acid agents, tissue buffers may reduce the ultimate extent of change. It is emphasised that the percentage inactivation here determined is an *in vitro* measurement which may overstate the true figure. It should also be remembered that, in general, penicillin dosage is not precisely adjusted to meet requirements. Thus possible minor effects, of the order of those with decicain and percaine, would not cause significant alteration in total dose. But clearly "Novutox" and even procaine are better avoided.

Analgesia for serial injections of penicillin: Intermittent injections, at intervals of up to three hours or more, may be given painlessly, except for the initial needle-prick, as follows:—To 1:1500 percaine, adrenaline hydrochloride (BP) is added to a concentration of 1:200,000. Penicillin is dissolved in sterile distilled water to a concentration of 10,000 units/cc.; 2.5 cc. of each solution are drawn up, making a final concentration in the syringe of 1:3000 percaine and 1:400,000 adrenaline. An area of skin 1 cm. in diameter is marked with iodine. At its centre, and using a hypodermic needle, an intra-cuticular wheal is raised with the mixture. The hypodermic needle is now replaced by an intra-muscular needle. This is pushed down through the wheal, injecting slowly as the needle point advances. About half of the first injection is allowed to flow just under the skin. This provides a pool of analgesic agent, which can be maintained by small additions at subsequent injections. Absolute analgesia persists for over three hours, and subsequent injections are made painlessly through the area marked; no further intra-cuticular wheal need be produced and, as has been shown, there is no significant loss of penicillin titre in the mixture.

SUMMARY

Commonly used anæsthetic agents and adrenaline have been mixed with penicillin and inactivation measured over an eight-hour period at body temperature. Deterioration of penicillin is not significantly increased by exposure to 1:3000 decicain, 1:3000 percaine or 1:200,000 adrenaline. But with 2% procaine, 1% cocaine, and "Novutox" increasing degrees of destruction occur. A painless method of giving penicillin injections intermittently is described.

[illegible]

SUGGESTED METHOD OF PENICILLIN ADMINISTRATION*

By Capt. O. G. Lane, RAMC, Resuscitation Officer, 110 (Br.) General Hospital

As most of the rubber in the glucose saline giving sets is synthetic rubber which may inactivate penicillin—and three-hourly injections become increasingly unpleasant and painful to most patients—the following method of administration of penicillin is suggested as a possible alternative.

To the end of a needle of the size used in intravenous giving sets is fitted a short piece of rubber tubing about 1″ in length. An adaptor is fitted to the end of the rubber tubing. A clip is placed round the rubber tubing.

The needle is inserted into the muscle and left there. Penicillin is given from a syringe which is fixed to the adaptor at the time of injection. The clip is kept closed at all times except when actually giving the penicillin. The clip is closed before removing the syringe. Three-hourly injections can thus be given without pain.

A small amount of local anæsthetic makes the insertion of the needle painless, and it is fixed in position with adhesive tape. The needle should be removed every 24 hours, sterilised, and inserted in a different place. The rubber tubing and adaptor should be enclosed in sterile gauze and a wad of sterile cotton wool placed over the whole area. In some cases after leaving the needle in one place for five days, swabs taken from the adaptor have been sterile. Sepsis which may start between the needle and the skin can be prevented by changing the place of the needle once in 24 hours.

We have found this method more satisfactory to the patient and the staff than either continuous drip or three-hourly injections.

* This communication was submitted on 3 November, 1944.

PENICILLIN BY INTRA-ORAL DRIP

By Maj. G. R. Royston, RAMC, Medical Specialist, and Capt. A. G. Deverell, RAMC, Pathologist

In order to provide a continuous local application of penicillin to oral and faucial infective conditions one of us (G. R. R.) devised a simple intra-oral drip apparatus.

It consists of the standard Army transfusion drip apparatus attached to a 7" length of thin soft rubber tubing, stiffened by a contained wire, thus enabling the tubing to be bent in the form of a hook of which the short limb lies in the buccogingival sulcus and the long limb along the cheek.

The solution used is 100,000 units of sodium penicillin in 500 ccs. of N/saline, and this is run in at the rate of 5-6 drops per minute, taking 24 hours per bottle. This caused no inconvenience to the patient apart from a bitter taste, noticed only for the first few hours. There was no conscious increase in swallowing and sleep was undisturbed. Treatment was usually continued for three days.

In all, about 70 cases have been treated, all diagnoses being confirmed by swabs taken prior to treatment. In the absence of full bacteriological control throughout treatment no claim is made that the above method is any advance on other well-tried therapeutic measures, but certain very definite clinical impressions were formed:—

1. Patients liked it.

2. Dramatic subjective relief and clinical improvement occurred in most cases of faucial and gingival Vincent's infection, improvement setting in within six hours of commencing the drip.

3. Gross streptococcal peritonsillar swelling, in some cases with pus formation, that had failed to respond to sulphathiazole, frequently responded to penicillin within 18 hours.

4. Diphtheria carriers of three weeks' duration could be rendered temporarily negative, but swabs always became positive again within 72 hours of cessation of treatment.

5. Local discomfort in severe faucial diphtheria and angiose glandular fever could be lessened.

To quote a typical example: A man with gross bilateral streptococcal peritonsillar swelling when first seen at 1700 hours could scarcely articulate and swallowed with great pain and difficulty. He was treated solely by the drip method, and the following morning the swelling was slightly less, though no pus had discharged, the fauces were less angry and the patient asked for bread and butter for his breakfast!

ADDENDUM

Since the above communication was written (March, 1945) we have carried out further experiments with this method. These investigations are not yet complete, but preliminary observations show that a total dosage of 100,000 units is needlessly large, and satisfactory results have been obtained using 50,000 units. We consider this is still too high, but have not yet established the optimum dosage.

SPECIAL PENICILLIN SYRINGES

By Maj. T. J. Burness, REME

Amongst the many problems faced by the RAMC in the earlier days of the Normandy invasion the administration of penicillin was not the least difficult. These difficulties were greatly increased at night under the strict black-out conditions then necessary, and it was well-nigh impossible to see the gradations on an ordinary syringe in tents dimly lit by hurricane lamps. Continuous methods of administration were hampered by the rapid turn-over of patients and were mainly used in cases that had to be held in the Units for one reason or another; the remainder in those early days had penicillin by intermittent injections.

Lt.-Col. N. J. Logie, RAMC, conceived the idea of using a reservoir syringe that, by a system of valves, would enable a series of 1 cc. injections to be given accurately even in the dimmest light. About 15 July, 1944 (D-39), he approached me and asked if the REME could help. This help was gladly given, and it was decided to attach a reservoir to an ordinary 5 cc. "Record" syringe. This reservoir was made from the barrel of an old telescope; one end was sealed and the other fitted with a fluid-tight cap. The metal of the nozzle end of the syringe was carefully drilled and tapped, and the two cone type brass valves were turned in the Instrument Shop. Two hair springs obtained from damaged watches were used to act as compressor springs for the valves. The valves were so arranged that during injections the solution in the reservoir was sealed off from the syringe barrel. It is interesting to record that the first modified syringe was produced in 39 hours in a Field Workshop under enemy fire, without a break other than for meals.

The syringe was tested by Lt.-Col. Logie and was reasonably satisfactory in use, but it was found that after a short period the valves tended to stick; this led to inaccuracies in the dosages given. About a fortnight later an improved model utilising the actual barrel as the reservoir and with one of the valves incorporated in the piston was suggested, and this was put into production forthwith. In this model clap-type fibre valves were

fitted, compression spring loaded, inside the piston and in the outlet nozzle. The dosage could be varied by altering the range of piston travel, the spindle being threaded and accurately marked for this purpose. All metal used in making the syringes was tested for its effect on penicillin by Maj. K. E. A. Hughes, RAMC.

Lt.-Col. Logie tested the new syringes and found them most satisfactory, and after a few minor modifications numbers were produced for distribution to Field Surgical and other Units. This Type D52 Mark I (capacity 20 ccs.), first produced 52 days after "D" day, proved very useful under certain conditions prevailing in Field Units, but various improvements were effected —finger-grip handles, heavier knurling on the thumb spindle, larger filling orifice, etc., and this improved model was designated Type D52 Mark II.

Another type (D137) was designed for use in hospitals. This syringe has a capacity of 26 ccs. and has external graduations giving sight readings of 1, 2 or 3 ccs., and these dosages can be pre-set by means of the accurately threaded piston spindle. This type has certain advantages. It has no filler orifice, but is filled like any ordinary syringe, this being made possible by the fitting of a quick release mechanism on the spindle; a half-turn anticlockwise releases the spindle, and a half-turn in the opposite direction locks it in any predetermined position to give the exact dosage required. This model, however, was unpopular, possibly because in use there was no means of discovering the amount of solution remaining in the barrel. A further type (D187) was therefore designed with a graduated external spindle which at all times gives a reading of the contents remaining in the syringe. A further improvement in this type was the introduction of a trigger movement.

This last model (D187) has a capacity of 26 ccs. with an external tell-tale spindle. When empty the spindle is inside the barrel. By withdrawing the spindle the syringe is filled with 26 ccs. penicillin solution. At the top end of the syringe an automatic indicator is fitted with graduations and a pointer to allow of 1, 1.5, 2, 2.5 or 3 ccs. dosages to be given at will. By pressing the trigger the predetermined dosage is injected, and at the same time the external graduated spindle, by decreasing inside the barrel with piston travel, gives a quick sight reading of the remaining contents of the syringe.

These syringes have played their part in helping the Army doctors to cope with the special problems created by the injection of penicillin under difficult circumstances in the field.

Appendix

SUMMARY OF SURGICAL RESULTS (FORWARD UNITS AND SPECIAL TEAMS), D-DAY TO VE-DAY

	Total Cases	Deaths	Percentage Recovery
Head Wounds — Meninges Penetrated	1248	125	89.9%
Head Wounds — Meninges not Penetrated	1258	32	97.5%
Maxillo-Facial Wounds	3501	53	98.5%
Chest — Penetrating or Perforating Wounds	2329	223	90.4%
Abdomen — Penetrating or Perforating Wounds with Intraperitoneal Visceral Injuries	3579	1065	70.2%
Abdominal Wounds with Extraperitoneal Visceral or Vascular Injuries or Intraperitoneal Haemorrhage	740	73	90.1%
Thoraco-Abdominal or Abdomino-Thoracic Wounds	786	333	57.6%
"Acute" Abdomens	632	7	98.9%
Upper Limb Amputations (Excluding Those Below Wrist)	552	18	96.7%
Lower Limb Amputations (Excluding Those Below Ankle)	2103	182	91.3%
Fractures of Spine with Cord Injuries	383	62	83.8%
Fractures of Spine: Cord Uninjured	126	3	97.6%
Open Fractures — Humerus	1714	12	99.3%
" — Radius and Ulna	1445	0	100.0%
" — Pelvis	336	18	94.6%
" — Femur	2364	108	95.4%
" — Tibia and Fibula	2825	19	99.3%
Open Joint Injuries — Shoulder	258	2	99.2%
" — Elbow	377	2	99.5%
" — Wrist	145	0	100.0%
" — Hip	53	0	100.0%
" — Knee	1365	7	99.5%
" — Ankle	313	0	100.0%
Burns (Less Than 20% Surface Affected)	603	0	100.0%
Burns (More Than 20% Surface Affected)	435	22	94.9%
Flesh Wounds	11021	55	99.5%
Flesh Wounds with Injuries of Main Nerves	807	1	99.9%
Flesh Wounds with Injuries of Main Vessels	1148	53	95.4%
Anaerobic Myositis	287	64	77.7%
Anaerobic Cellulitis	62	6	90.2%
Miscellaneous	7406	19	99.7%
Grand Totals:—	50201	2564	94.9%

EXPLANATORY NOTES

1. The above figures were compiled from the monthly surgical reports submitted to the Consulting Surgeon, 21 Army Group, by Forward Units and Special Teams. Over the whole period (6 June, 1944, to 8 May, 1945) approximately 3% of these reports were not received, and the figures are therefore a slight underestimate of the total work. At the time of going to press the corresponding figures for base hospitals are not available.

2. Surgeons were asked to classify casualties under the heading of their major injury, and the great majority appear only under one heading. A small minority with two or more injuries of almost equal severity were shown under separate headings and the figures, therefore, represent lesions rather than cases; the numbers scattered through the groups are too small to produce any significant effect on the averages. For example, a man with a penetrating abdominal wound and a fractured pelvis was normally classified as an abdominal case, and open pelvic fractures were only recorded separately if they were unusually severe or unassociated with visceral damage.

3. Head Wounds: The fact that the meninges were not penetrated does not necessarily mean there was no cerebral damage. The figures give the results for the cases operated upon in this theatre, and do not include those dying before operation was possible or those others evacuated to the UK for operation.

4. Chest Wounds: Only cases with penetration or perforation of the pleura are included under this heading. Parietal wounds were classified as "flesh wounds", or as "miscellaneous" if there were associated scapular, sternal or rib fractures.

5. Abdominal Wounds: Laparotomies were performed in all cases recorded under this heading. Parietal wounds are not included here but are classified as "flesh wounds". All deaths occurring before evacuation from this theatre to the UK have been accounted for by cross checking the "Reports on Deaths" submitted by all units with those abdominal cases reported by the individual units concerned. Further information about the abdominal cases is given in the article "Penicillin in Abdominal Wounds".

6. Thoraco-Abdominal Wounds: Men with coincident thoracic and abdominal wounds were not classified as thoraco-abdominal or abdomino-thoracic. The deciding factor was the fact that the same missile had passed from chest to abdomen, or vice versa.

7. "Acute" Abdomens: The majority of these were cases of appendicitis, but naturally there were also perforated ulcers, strangulations, cases of obstruction, two cases of pancreatitis, etc.

8. Amputations: To avoid obtaining false mortality figures, amputations below the level of the wrist or ankle are not included in this section. Partial amputations of the hands and feet and of fingers and toes are relegated to the "miscellaneous" group.

9. Flesh Wounds: Only those actually operated upon were recorded. The majority, therefore, are of the more serious types. During a battle forward surgeons seldom have time to deal with minor wounds, and these are "screened" off and treated in the Field Dressing Station working in conjunction with the Casualty Clearing Station or Advanced Surgical Centre.

10. Anaerobic Myositis: Further information about these cases is given in the article on "Anaerobic Myositis in 21 Army Group."

11. Miscellaneous: This group includes a wide variety of conditions—dislocations; simple fractures; fractures of the scapula, sternum, hand and foot bones; neck wounds; minor amputations; septic hands, carbuncles, lymphangitis, cellulitis, bursitis; etc; eye injuries; crush injuries of the chest and abdomen; diseases such as appendicitis, strangulated hernia, perforated ulcers, volvulus, acute obstruction, etc., not specifically differentiated by surgeons in their reports; and a few cases of malignant disease.

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